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Original research paper

Synthesis and potential biological activity of some novel 3-[(*N*-substituted indol-3-yl)methyleneamino]-6-amino-4-aryl-pyrano(2,3-*c*)pyrazole-5-carbonitriles and 3,6-diamino-4-(*N*-substituted indol-3-yl)pyrano(2,3-*c*)pyrazole-5-carbonitriles

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Starting from *N*-substituted indole-3-carboxaldehydes (**1a**-**g**) a series of new 3-[(*N*-substituted indol-3-yl)methyleneamino]-6-amino-4-aryl-pyrano(2,3-*c*)pyrazole-5-carbonitriles (**3a**-**g** and **4a**-**g**) have been synthesized *via* the acid catalyzed condensation reaction of **1a**-**g** with 3-amino-5-pyrazolone, followed by the reaction with arylidene malononitriles. A series of new 3,6-diamino-4-(*N*-substituted indol-3-yl)pyrano(2,3-*c*)pyrazole-5-carbonitriles (**7a**-**g**) have been prepared either *via* the base catalyzed condensation reaction of **1a**-**g** with 3-amino-5-pyrazolone to give **6a**-**g**, followed by the reaction with malononitrile or by the reaction of *N*-substituted-3-indolylidene malononitriles (**5a**-**g**) with 3-amino-5-pyrazolone. According to the obtained results, the newly synthesized compounds possess significant anti-inflammatory, analgesic and anticonvulsant activities. The anticonvulsant potency of certain tested compounds was more pronounced than both anti-inflammatory and analgesic activities. Moreover, most of the newly synthesized compounds possess potential antimicrobial activity against *Escherichia coli* and *Pseudomonas aeruginosa.*

Keywords: indole, pyrano(2,3-*c*)pyrazole, anti-inflammatory, analgesic, anticonvulsant, antimicrobial activity

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Indole, the potent basic pharmacodynamic nucleus, has been reported to possess a wide variety of biological properties, *viz*, anti-inflammatory (1–3), anticonvulsant (4), analgesic (5) and antimicrobial (6, 7). Furthermore, substitution of heterocyclic moieties at position-3 of indole markedly influences the anti-inflammatory activity (5). Pyrazole and pyrano(2,3-*c*)pyrazole derivatives have also been reported to possess anti-inflammatory (8, 9) and antimicrobial activity (10). There has been considerable interest in developing synthetic methods for 6-amino-5-cyano-dihydropyrano(2,3-*c*)pyrazoles (11–13).

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These compounds may be readily obtained from the reaction of 4-aryl methylene--5-pyrazolone and malononitrile (11, 12) or 2-pyrazolin-5-one and benzylidene malononitrile (12). In the light of these interesting biological activities and also in continuation of our search (5, 6) for compounds potent as anti-inflammatory, analgesic, anticonvulsant agents and antimicrobials, we decided to synthesize some new pyrano(2,3-*c*)pyrazole-5-carbonitriles, attached directly or through the methyleneamino group bridge to *N*-substituted indoles at 3-position.

EXPERIMENTAL

Melting points were determined in open capillary tubes on an Electrothermal 9100 digital melting point apparatus (Büchi, Switzerland) and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 analyzer (Perkin-Elmer, USA) and were found within ± 0.4 % of the theoretical values (Table I). IR spectra were recorded on a Perkin-Elmer 1600 FTIR (Perkin-Elmer) in KBr discs. ^{1}H NMR spectra were measured on a Jeol 270 MHz spectrometer (Jeol, Japan) and a Bruker Avance spectrometer (300 MHz) (Bruker, Germany) in DMSO-d_6, and chemical shifts were recorded in δ ppm relative to the internal standard TMS. Mass spectra (EI) were run on a sector-fild mass spectrometer (AMD-Intectra GmbH, Germany) and a gas chromatograph/mass spectrometer, single phase, 200 V, 50/60 Hz, 30 A (Jeol). Spectral data of the synthesized compounds are listed in Table II.

The *N*-substituted indole-3-carboxaldehydes (**1a-g**) and *N*-substituted-3-indolylidene malononitriles (**5a-g**) were prepared as reported, respectively (14, 15). Synthetic paterns are given in Schemes 1 and 2.

Synthesis. General procedures

*3-[(*N*-substituted-1*H*-indol-3-yl)methyleneamino]-1*H*-pyrazol-5(4*H*)-ones (**2a-g**).* – A solution of compound **1a-g** (0.01 mol) and 3-amino-5-pyrazolone (0.99 g, 0.01 mol) in absolute ethanol (20 mL) containing a few drops of glacial acetic acid was refluxed for 2–3 h. After cooling, the solid that formed was filtered off, washed with water, air dried and recrystallized from ethanol.

*3-[(*N*-substituted-indol-3-yl)methyleneamino]-6-amino-4-(p-fluorophenyl) pyrano(2,3-c)pyrazole-5-carbonitriles (*3a-g*) and 3-[(*N*-substituted-indol-3-yl)methyleneamino]-6-amino-4-(*p*-chlorophenyl)pyrano(2,3-c)pyrazole-5-carbonitriles (**4a-g**).* – A mixture of compound **2a-g** (0.005 mol) and *p*-fluorobenzylidene malononitrile and/or *p*-chlorobenzylidene malononitrile (0.005 mol) in absolute ethanol (20 mL) containing triethylamine (0.5 mL) was refluxed for 3–4 h. The formed precipitate hot was filtered off hot, air dried and recrystallized from ethanol.

*4-[(*N*-substituted-indol-3-yl)methylene]-3-amino-1*H*-pyrazol-5(4*H*)-ones (**6a-g**).* – To a stirred solution of 3-amino-5-pyrazolone (0.99 g, 0.01 mol) in absolute ethanol (20 mL) containing triethylamine (0.5 mL), the appropriate *N*-substituted indole-3-carboxaldehyde (**1a-g**) (0.01 mol) was added. The reaction mixture was refluxed for 1–4 h. After cooling, the formed solid was filtered off, washed with water, air dried and recrystallized from ethanol.

Table I. Physical and analytical data of the prepared compounds

Compd. No.	Formula (M_r)	M.p. (°C)	Yield (%)	Analysis (calcd. /found) (%)		
				C	H	N
2a	$C_{12}H_{10}N_4O$ (226.23)	229–231	98	63.71/63.60	4.42/4.20	24.77/24.50
2b	$C_{14}H_{14}N_4O$ (254.29)	193–195	72	66.14/66.00	5.51/5.30	22.04/22.30
2c	$C_{19}H_{14}N_4O_2$ (330.34)	180–182	82	69.09/69.00	4.24/4.01	16.96/16.79
2d	$C_{19}H_{13}ClN_4O_2$ (364.79)	142–144	93	62.55/62.30	3.56/3.24	15.36/15.15
2e	$C_{19}H_{13}ClN_4O_2$ (364.79)	178–180	90	62.55/62.35	3.56/3.70	15.36/15.50
2f	$C_{18}H_{14}N_4O_3S$ (366.39)	140–142	82	59.01/59.20	3.82/3.50	15.30/15.50
2g	$C_{18}H_{13}BrN_4O_3S$ (445.29)	147–149	87	48.53/48.50	2.92/2.90	12.58/12.30
3a	$C_{22}H_{13}FN_6O$ (396.38)	135–137	85	66.66/66.50	3.28/3.20	21.21/21.00
3b	$C_{24}H_{17}FN_6O$ (424.43)	181–183	90	67.92/67.80	4.00/4.10	19.81/19.90
3c	$C_{29}H_{17}FN_6O_2$ (500.48)	164–166	72	69.60/69.50	3.40/3.51	16.80/16.91
3d	$C_{29}H_{16}ClFN_6O_2$ (534.93)	173–175	83	65.10/65.15	2.99/2.80	15.71/15.50
3e	$C_{29}H_{16}ClFN_6O_2$ (534.93)	152–152	89	65.18/65.40	2.99/3.01	15.71/15.60
3f	$C_{28}H_{17}FN_6O_3S$ (536.54)	177–179	75	62.68/62.50	3.17/3.30	15.67/15.80
3g	$C_{28}H_{16}BrFN_6O_3S$ (615.43)	152–154	81	54.63/54.45	2.60/2.43	13.65/13.66
4a	$C_{22}H_{13}ClN_6O$ (412.83)	283–285	81	64.00/64.11	3.15/3.21	20.36/20.22
4b	$C_{24}H_{17}ClN_6O$ (440.88)	276–278	77	65.38/65.20	3.85/3.73	19.06/19.21
4c	$C_{29}H_{17}ClN_6O_2$ (516.94)	270–272	71	67.37/67.20	3.29/3.17	16.26/16.00
4d	$C_{29}H_{16}Cl_2N_6O_2$ (551.38)	130–132	72	63.15/63.34	2.90/2.74	15.24/15.15
4e	$C_{29}H_{16}Cl_2N_6O_2$ (551.38)	114–116	75	63.15/63.30	2.90/2.81	15.24/15.51
4f	$C_{28}H_{17}ClN_6O_3S$ (552.99)	115–117	80	60.81/60.50	3.07/2.93	15.20/15.30
4g	$C_{28}H_{16}BrClN_6O_3S$ (631.89)	165–167	82	53.20/53.00	2.53/2.70	13.30/13.50
6a	$C_{12}H_{10}N_4O$ (226.23)	185–187	90	63.71/63.55	4.42/4.33	24.77/24.55
6b	$C_{14}H_{14}N_4O$ (254.29)	118–120	95	66.14/66.19	5.51/5.45	22.04/22.15
6c	$C_{19}H_{14}N_4O_2$ (330.34)	210–212	69	69.09/69.00	4.24/4.00	16.96/16.80
6d	$C_{19}H_{13}ClN_4O_2$ (364.79)	158–160	78	62.55/62.33	3.56/3.34	15.36/15.22
6e	$C_{19}H_{13}ClN_4O_2$ (364.79)	238–240	75	62.55/62.33	3.56/3.42	15.36/15.50
6f	$C_{18}H_{14}N_4O_3S$ (366.39)	161–163	82	59.01/59.11	3.82/3.77	15.30/15.44
6g	$C_{18}H_{13}BrN_4O_3S$ (445.29)	156–158	80	48.53/48.59	2.92/2.88	12.58/12.66
7a	$C_{15}H_{10}N_6O$ (290.28)	254–256	63[a]/33[b]	62.06/62.11	3.44/3.50	28.96/28.70
7b	$C_{17}H_{14}N_6O$ (318.33)	282–284	68[a]/47[b]	64.15/64.00	4.40/4.33	26.41/26.55
7c	$C_{22}H_{14}N_6O_2$ (394.39)	135–137	40[a]/23[b]	67.00/67.11	3.55/3.44	21.31/21.20
7d	$C_{22}H_{13}ClN_6O_2$ (428.83)	176 dec.	51[a]/25[b]	61.61/61.44	3.03/3.01	19.60/19.45
7e	$C_{22}H_{13}ClN_6O_2$ (428.83)	220 dec.	52[a]/24[b]	61.61/61.55	3.03/3.11	19.60/19.50
7f	$C_{21}H_{14}N_6O_3S$ (430.44)	160–162	51[a]/32[b]	58.60/58.55	3.25/3.33	19.53/19.33
7g	$C_{21}H_{13}BrN_6O_3S$ (509.34)	186–188	54[a]/20[b]	49.50/49.33	2.55/2.66	16.50/16.66

[a] The overall yield obtained by method A.
[b] The overall yield obtained by method B.

Table II. Spectral characterization of the new compounds

Compd. No.	IR (ν_{max}, cm^{-1})	^1H NMR (δ, ppm)	MS (*m/z*, %)
2a	3295 (NH), 1671 (C=O), 1616 (C=N), 1569 (C=C)	11.4, 10.2 (2s, 2H, 2NH), 8.54 (s, 1H, CH=N), 7.1–8.1 (m, 5H, Ar-H), 4.6 (s, 2H, CH_2)	226 (M^+, 9), 142 (6), 117 (100), 91(10), 77 (16), 76 (18)
2b	3178 (NH), 1685 (C=O), 1611 (C=N), 1536 (C=C)	11.4 (s, 1H, NH), 8.54 (s, 1H, CH=N), 7.18–8.16 (m, 5H, Ar-H), 4.2 (s, 2H, CH_2-pyrazole), 3.75 (q, 2H, CH_2), 1.38 (t, 3H, CH_3)	
2c	3250 (NH), 1703 (C=O), 1658 (C=N), 1598 (C=C)		
2d	3373 (NH), 1651 (C=O), 1591 (C=N), 1576 (C=C), 744 (Cl)	12.1 (s, 1H, NH), 8.57 (s, 1H, CH=N), 7.01–8.1 (m, 9H, Ar-H), 4.3 (s, 2H, CH_2)	364 (M^+, 1), 366 (M^++2, 0.2), 226 (14), 139 (18), 142 (10), 117 (100)
2e	3356 (NH), 1682 (C=O), 1591(C=N), 1544 (C=C), 757 (Cl)		
2f	3411 (NH), 1677 (C=O), 1599 (C=N), 1542 (C=C), 1375, 1173 (SO_2)	11.8 (s, 1H, NH), 8.4 (s, 1H, CH=N), 7.3–8.3 (m, 10H, Ar-H), 4.2 (s, 2H, CH_2)	
2g	3414 (NH), 1685 (C=O), 1645 (C=N), 1561 (C=C), 1387, 1173 (SO_2), 746 (Br)	11.8 (s, 1H, NH), 8.45 (s, 1H, CH=N), 7.8–8.3 (m, 9H, Ar-H), 3.8 (s, 2H, CH_2)	
3a	3353 (NH_2, NH), 2211 (CN), 1603 (C=N), 1553 (C=C), 1014 (C-O-C)	9.9 (s, 1H, NH indole), 8.5 (s, 1H, CH=N), 7.0–7.6 (m, 9H, Ar-H), 2.7 (s, 2H, NH_2)	
3b	3402, 3299 (NH_2), 2210 (CN), 1661 (C=N), 1592 (C=C), 1090 (C-O-C)	8.5 (s, 1H, CH=N), 7.2–8.02 (m, 9H, Ar-H), 5.9 (s, 2H, NH_2), 4.2 (q, 2H, CH_2), 1.6 (t, 3H, CH_3)	
3c	3326 (NH_2, br), 2210 (CN), 1779 (C=O), 1604 (C=N), 1556 (C=C), 1015 (C-O-C)	8.71 (s, 1H, CH=N), 7.0–8.2 (m, 14H, Ar-H), 5.8 (s, 2H, NH_2)	
3d	3386 (NH_2), 2204 (CN), 1650 (C=O), 1604 (C=N), 1570 (C=C), 1015 (C-O-C), 745 (Cl)		
3e	3354, 3206 (NH_2), 2204 (CN), 1757 (C=O), 1638 (C=N), 1598 (C=C), 1016 (C-O-C), 742 (Cl)	8.7 (s, 2H, NH_2), 8.5 (s, 1H, CH=N), 8.0 (s, 1H, H-2 indole), 7.3–7.6 (m, 12H, Ar-H)	
3f	3372 (NH_2), 2208 (CN), 1605 (C=N), 1509 (C=C), 1372, 1175 (SO_2), 1019 (C-O-C)	8.5 (s, 1H, CH=N), 7.2-7.9 (m, 14H, Ar-H), 2.7 (s, 2H, CH_2)	
3g	3357 (NH_2), 2204 (CN), 1617 (C=N), 1567 (C=C), 1377, 1176 (SO_2), 1012 (C-O-C), 747 (Br)		536 (M^+-Br, 8), 396 (52), 320 (43), 142 (23), 127 (100)

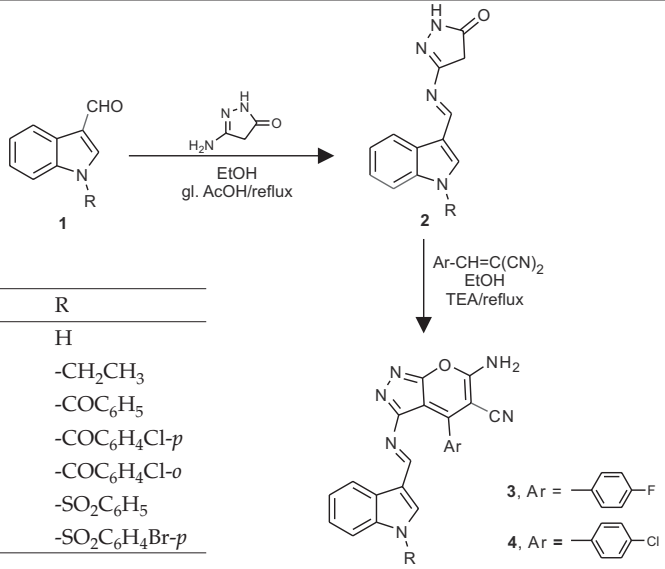
4a	3381, 3308 (NH_2), 3200 (NH), 2214 (CN), 1629 (C=N), 1530 (C=C), 1094 (C-O-C), 746 (Cl)	12.1 (s, 1H, NH), 8.7 (s, 1H, CH=N), 7.1–8.2 (m, 9H, Ar-H), 4.3 (s, 2H, NH_2)	
4b	3291(NH_2), 2208 (CN), 1651 (C=N), 1589 (C=C), 1196 (C-O-C), 742 (Cl)	8.7 (s, 1H, CH=N), 8.2 (s, 1H, H-2 indole), 7.2–7.6 (m, 8H, Ar-H), 6.1 (s, 2H, NH_2), 4.3 (q, 2H, CH_2), 1.4 (t, 3H, CH_3)	440 (M^+, 1), 442 (M^++2, 0.2), 145 (53), 130 (100), 117 (21)
4c	3382, 3308 (NH_2), 2216 (CN), 1666 (C=O), 1628 (C=N), 1530 (C=C), 1009 (C-O-C), 751 (Cl)		
4d	3337 (NH_2), 2212 (CN), 1703 (C=O), 1620 (C=N), 1575 (C=C), 1014 (C-O-C), 746 (Cl)	8.7 (s, 2H, NH_2), 8.5 (s, 1H, CH=N), 7.3–8.1 (m, 14 H, Ar-H)	
4e	3338 (NH_2), 2214 (CN), 1621 (C=N), 1565 (C=C), 1013 (C-O-C), 748 (Cl)	8.7 (s, 2H, NH_2), 8.5 (s, 1H, CH=N), 8.05 (s,1H, H-2 indole), 7.3–7.6 (m, 12H, Ar-H)	
4f	3356 (NH_2), 2203 (CN), 1665 (C=N), 1572 (C=C), 1373, 1175 (SO_2), 1014 (C-O-C), 746 (Cl)		552 (M^+, 1), 554 (M^++2, 0.2), 282 (9), 256 (10), 130 (33), 117 (80), 109 (100)
4g	3375 (NH_2), 2210 (CN), 1625 (C=N), 1566 (C=C), 1366, 1157 (SO_2), 1013 (C-O-C), 747 (Br), 702 (Cl)	8.5 (s, 1H, CH=N), 7.2–8.0 (m, 13H, Ar-H), 5.61 (s, 2H, NH_2)	
6a	3392 (NH_2), 3180 (NH), 1671 (C=O), 1594 (C=N), 1523 (C=C)		
6b	3290 (NH_2), 3179 (NH)), 1654 (C=O), 1592 (C=N), 1502 (C=C)		
6c	3403, 3284 (NH_2), 3218 (NH), 1645 (C=O), 1621 (C=N), 1590(C=C)		
6d	3358 (NH_2), 3202 (NH), 1644 (C=O), 1586 (C=N), 1523 (C=C), 736 (Cl)		
6e	3296 (NH_2), 3203 (NH), 1645 (C=O), 1588 (C=N), 1523 (C=C), 733 (Cl)		364 (M^+, 1), 366 (M^++2, 0.2), 226 (100), 117 (93), 115 (95)
6f	3207 (NH_2, NH, br), 1625 (C=O), 1586 (C=N), 1523 (C=C), 1370, 1175 (SO_2)		
6g	3319 (NH_2) 3195 (NH), 1603 (C=O), 1577 (C=N), 1503 (C=C), 1375, 1174 (SO_2), 747 (Br)	10.37 (s, 1H, NH), 8.89 (s, 1H, H-2 indole), 7.25–7.93 (m, 8H, Ar-H), 5.98 (s, 1H, CH=C), 5.75 (s, 2H, NH_2)	

7a	3243 (NH_2), 3164 (NH), 2211 (CN), 1640 (C=N), 1617 (C=C), 1044 (C-O-C)	9.0 (s, 1H, NH indole), 8.1 (s, 1H, H-2 indole), 7.5–7.9 (m, 4H, Ar-H), 6.9 (s, 2H, NH_2), 3.8 (s, 2H, NH_2)	290 (M^+, 2), 159 (10), 143 (50), 142 (100), 117 (76)
7b	3321, 3184 (NH_2), 2205 (CN), 1664 (C=N), 1602 (C=C), 1197(C-O-C)		318 (M^+, 7), 159 (100), 157 (20), 117 (14), 91 (32)
7c	3429, 3317 (NH_2), 2206 (CN), 1735 (C=O), 1629 (C=N), 1582 (C=C), 1106 (C-O-C)	11.88 (s, 2H, NH_2), 8.34 (s, 1H, H-2 indole), 7.84 (s, 2H, NH_2), 7.1–7.5 (m, 9H, Ar-H)	
7d	3426, 3316 (NH_2), 2203 (CN), 1626 (C=O), 1585 (C=N), 1508 (C=C), 1106 (C-O-C), 755 (Cl)		428 (M^+, 100), 430 (M^++2, 30) 193 (40), 117 (50), 91 (40)
7e	3429, 3316 (NH_2), 2204 (CN), 1628 (C=O), 1683 (C=N), 1552 (C=C), 1106 (C-O-C), 755 (Cl)		
7f	3324 (NH_2, br), 2212 (CN), 1620 (C=N), 1573 (C=C), 1368, 1130 (SO_2), 1106 (C-O-C)	11.9, 5.9 (2s, 4H, $2NH_2$), 8.25 (s, 1H, H-2 indole), 7.1– 8.1 (m, 9H, Ar-H)	
7g	3324 (NH_2, br), 2212 (CN), 1618 (C=N), 1522 (C= C), 1376, 1176 (SO_2), 1128 (C-O-C), 748 (Br)	9.9, 5.7 (2s, 4H, $2NH_2$), 8.3 (s, 1H, H-2 indole), 7.2–7.9 (m, 8H, Ar-H)	508 (M^+, 37), 510 (M^++2, 36) 348 (100), 219 (53), 155 (47), 77 (77)

*3,6-Diamino-4-(*N*-substituted-indol-3-yl)pyrano(2,3-c)pyrazole-5-carbonitriles (**7a-g**). Method A*. – A mixture of 3-amino-5-pyrazolone (0.99 g, 0.01 mol) and the appropriate *N*-substituted-3-indolylidene malononitrile **5a-g** (0.01 mol) in absolute ethanol (20 mL) containing triethylamine (0.5 mL) was refluxed for 1–4 h. The formed precipitate was filtered off after cooling, air dried and recrystallized from dioxane. *Method B*. – To a solution of malononitrile (0.66 g, 0.01 mol) in absolute ethanol (10 mL) and triethylamine (0.5 mL), the appropriate compound **6a-g** (0.01 mol) was added. The reaction mixture was refluxed for 3–4 h, and the solid that formed after cooling was filtered off, air dried and recrystallized from dioxane.

Biological assays

Animals. – Adult male albino rats (Harlan Sprague-Dawley), weighing 150–180 g, were used for the evaluation of anti-inflammatory activity. Animals were fasted for 12 hours before the assay. Adult Swiss Webster mice of both sexes (Harlan Sprague-Dawley), weighing 20–25 g, were fasted for 12–24 hours and used for the assessment of analgesic and anticonvulsant activities. All animals were obtained from the animal house colony of the National Research Centre, Cairo, Egypt. Animals were allowed free access to water and were fed a standard diet. Research was conducted in accordance with the ethical rules on animal experimentation, approved by the Ethics Committee of the National Research Centre, Cairo, Egypt.



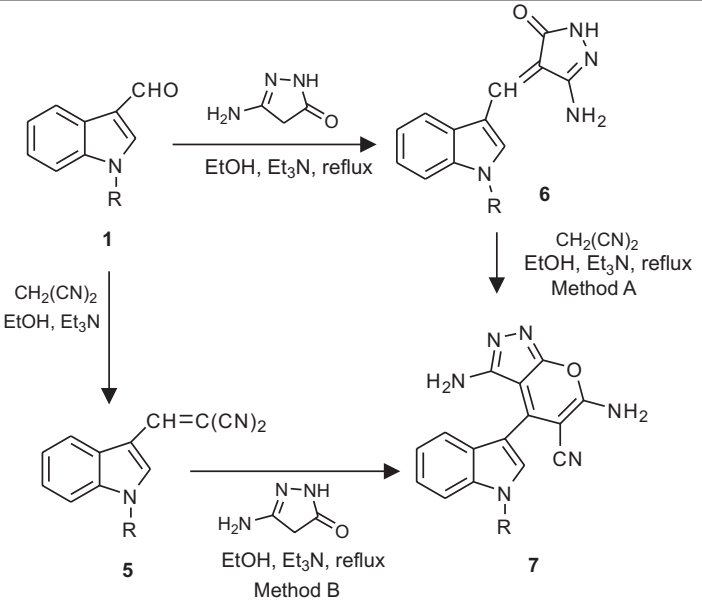
1–4	R
a	H
b	-CH_2CH_3
c	-COC_6H_5
d	-COC_6H_4Cl-*p*
e	-COC_6H_4Cl-*o*
f	-$SO_2C_6H_5$
g	-$SO_2C_6H_4Br$-*p*

Scheme 1

Anti-inflammatory activity. – Evaluation of the anti-inflammatory activity was performed using carrageenean-induced rat's paw oedema model according to the method of Obkowicz *et al.* (16). The animals were divided into groups (control, reference and test groups) of 8 animals each. Acute inflammation was produced by subplantar injection of 0.05 mL of 1 % suspension of carrageenean in saline into the plantar tissue of one (right) hind paw of the rat, one hour after oral administration of the test compound at dose levels of 20 and 5 mg kg^{-1}. The control group received an equal volume of saline into the other (left) hind paw. The reference group was orally administered flufenamic acid (20 mg kg^{-1}) and indomethacin (5 mg kg^{-1}) suspended in saline as reference drugs. The average mass of oedema was estimated for the control, reference and test groups four hours after drug administration. The inhibitory activity (percentage of inhibition of oedema) was evaluated (17).

The results were analyzed for statistical significance (expressed as mean ± SEM) between the vehicle control and treated groups using one-way ANOVA followed by multiple comparisons by Duncan's multiple range tests.

Analgesic activity. – It was studied using the *p*-benzoquinone-induced writhing model in mice according to the method described by Okun *et al.* (18). The test compounds and reference drugs flufenamic acid and indomethacine were prepared as a suspension in 2 % Tween 80. A sensitivity test was carried out one day before drug administration when the animals were injected (*i.p.*) 0.2–0.25 mL of 0.02 % freshly prepared solution of *p*-benzoquinone in distilled water. Animals showing writhing to *p*-benzoquinone within 30 minutes were chosen to study the analgesic activity. On the following day, mice were divided into 13 groups of 6 animals each, and the drugs were administered according to



1–7	R
a	H
b	-CH_2CH_3
c	-COC_6H_5
d	-COC_6H_4Cl-*p*
e	-COC_6H_4Cl-*o*
f	-$SO_2C_6H_5$
g	-$SO_2C_6H_4Br$-*p*

Scheme 2

the following protocol: one group received 2 % Tween 80 (solvent negative control), the second group received flufenamic acid as reference (20 mg kg^{-1}), the third group received indomethacine as reference (5 mg kg^{-1}), while the other groups received two doses of test compounds (20 and 5 mg kg^{-1}). One hour latter, a 0.02 % solution of *p*-benzoquinone was administered (*i.p.*). The animals were observed for 30 minutes after injection of the irritant, during which time the animals showing writhing were counted (writhing is defined as stretching, torsion to one side, drawing up of hind leg, retraction of the abdomen, so that the mouse belly touches the floor). All writhing is considered as a positive response. The analgesic activity was expressed as percent protection.

Anticonvulsant activity. – The electric shock seizure test (19) was taken as the criterion for the evaluation of anticonvulsant activity. Mice were injected intraperitoneally with 2 % Tween 80 (solvent, negative control) and 5 mg kg^{-1} diazepam (reference drug). The other groups received two doses (25 and 12.5 mg kg^{-1}) of each test compound. One hour after drug administration, animals were stimulated through an ear electrode of 50 mA as a signal stimulator for 0.2 s. The characteristic of electric shock seizure is a tonic limb flexion of 1 to 2 s, followed by a tonic limb extension of roughly 10 to 12 s, and finally generalized clonic movement for 12 s. Only abolishment of the hind limb tonic extensor spasm is recorded as the measure of anticonvulsant potency. The tonic component is considered abolished if the hind leg extension does not exceed a 90° angle with the plane of the body. Animals showing protection against convulsion were counted in each group. The anticonvulsant activity was expressed as percent protection.

Antimicrobial evaluation. – Antimicrobial activity of the synthesized compounds was determined *in vitro* using the disc diffusion method (20) against pathogenic microorganisms: *Escherichia coli*, *Pseudomonas aeruginosa* (Gram-negative bacteria), *Staphylococcus aureus*, *Bacillus cereus* (Gram-positive bacteria) and one strain of fungi (*Candida albicans*). They were isolated from clinical samples and identified to the species level according to the API 20E system (Analytab Products, Inc., USA) (bioMerieux, Australia). Antimicrobial activities of the test compounds were estimated by placing presterilized filter paper discs (6 mm in diameter) impregnated with different doses of test compounds (100, 50 and 25 μg per disc) on nutrient and MacConky agar media for bacteria and on Sabouraud dextrose agar for the fungus. Dimethyl formamide (DMF) was used as a solvent for impregnation. Inhibition zones of the tested compounds were measured after 24–48 h. incubation at 37 °C for bacteria and after 5 days of incubation at 28 °C for fungi. Cefotaxime (CTX), a standardized 30 μg CTX disc was used in the disc diffusion test (Hoechst-Roussel Pharmaceuticals, Germany) and piperacillin (Piperacillin (PIP) 100 μg per disc (Bristol-Myers Squibb, Egypt) were used as reference drugs for bacteria, while nystatin (30 units per disc) (Bristol-Myers Squibb) (unit = 0.04 μg per disc) was used as reference drug for the fungi.

RESULTS AND DISCUSSION

Chemistry

Acid catalyzed reaction of *N*-substituted indole-3-carboxaldehydes (**1a**-**g**) with 3-amino-5-pyrazolone under reflux in absolute ethanol led to the formation of new Schiff's bases, 3-[(*N*-substituted-1*H*-indol-3-yl)methyleneamino]-1*H*-pyrazol-5(4*H*)-ones (**2a**-**g**) (Scheme 1). Condensation of the latter compounds with arylidene malononitrile, namely, *p*-fluorobenzylidene malononitrile and/or *p*-chlorobenzylidene malononitrile in refluxing ethanol and in the presence of a base afforded new 3-[(*N*-substituted-indol-3-yl)methyleneamino)-6-amino-4-(*p*-fluorophenyl]pyrano(2,3-c)pyrazole-5-carbonitriles (**3a**-**g**) and 3-[(*N*-substituted-indol-3-yl)methyleneamino]-6-amino-4-(*p*-chlorophenyl)pyrano (2,3-c)pyrazole-5-carbonitriles (**4a**-**g**), respectively (Scheme 1). The reaction proceeded through addition of active methylene groups of compounds **2a**-**g** to the ethylenic double bond of *p*-fluoro(*p*-chloro)benzylidene malononitriles, followed by intramolecular cyclization and aromatization to give **3a**-**g** and **4a**-**g**.

The structure of compounds **3a**-**g** and **4a**-**g** was supported by their precise elemental analyses (Table I) and spectral data (Table II). As an example, the IR spectrum of compound **4b** showed absorption bands at 3291 (NH_2), 2208 (CN), 1651 (C=N), 1589 (C=C), 1196 (C-O-C) and 742 cm^{-1} (Cl). Its ^1H NMR spectrum revealed signals at 6.1 (s, 2H, NH_2, exchangeable with D_2O), 8.7 (s, 1H, CH=N), 8.2 (s, 1H, H-2 indole), 7.2–7.6 (m, 8H, Ar-H), 4.3 (q, 2H, CH_2) and 1.4 ppm (t, 3H, CH_3). Its mass spectrum showed the molecular ion peak at *m/z* = 440 (M^+, 1), 442 (M^++2, 0.2) and a base peak at *m/z* = 130.

On the other hand, the base catalyzed Knovenagel reaction of **1a**-**g** with 3-amino-5-pyrazolone yielded the new 4-[(*N*-substituted-indol-3-yl)methylene]-3-amino-1*H*-pyrazol-5(4*H*)-ones (**6a**-**g**) in good yields (69–95 %, Scheme 2). Condensation of the latter compounds with malononitrile in refluxing ethanol containing triethylamine led to the

formation of new 3,6-diamino-4-(*N*-substituted-indol-3-yl) pyrano(2,3-*c*)pyrazole-5-carbonitriles (**7a-g**) (method A) with the overall yield of 40–68 %. Moreover, compounds **7a-g** could also be obtained with an overall yield of 20–47 % *via* the condensation reaction of *N*-substituted indole-3-carboxaldehyde (**1a-g**) with malononitrile to give *N*-substituted indolylidene malononitriles (**5a-g**), which reacted with 3-amino-5-pyrazolone in refluxing absolute ethanol containing triethylamine (method B) (Scheme 2). The reaction proceeded *via* addition of an active methylene group of malononitrile to the ethylenic double bond of compounds **6a-g** (method A) or addition of an active methylene group

Table III. Activity of compounds on carrageenean induced rats paw oedema

Compd. No.	Dose (mg kg^{-1})	Inhibition (%)	Compd. No.	Dose (mg kg^{-1})	Inhibition (%)
2a	5	24	**4d**	5	27
	20	39		20	42
2d	5	20	**4e**	5	33
	20	28		20	45
2e	5	25	**4f**	5	26
	20	37		20	33
2g	5	19	**4g**	5	32
	20	24		20	39
3a	5	19	**6a**	5	39
	20	20		20	32
3b	5	16	**6b**	5	16
	20	27		20	50
3c	5	19	**6e**	5	39
	20	45		20	32
3d	5	24	**6g**	5	16
	20	34		20	50
3e	5	19	**7a**	5	19
	20	34		20	24
3f	5	16	**7d**	5	25
	20	45		20	37
3g	5	19	**7e**	5	28
	20	27		20	42
4a	5	19	**7g**	5	26
	20	24		20	34
4b	5	19	Negative control[a]	0	0
	20	39			
4c	5	24	Flufenamic acid[a]	20	53
	20	28	Indomethacin[a]	5	51

[a] Saline is a negative control, also solvent for test compounds and reference drugs.

of 3-amino-5-pyrazolone to the ethylenic double bond of compounds **5a-g** (method B), followed by intramolecular cyclization and aromatization to give **7a-g.**

The structure of compounds **7a-g** was supported by their elemental analyses (Table I) and spectral data (Table II). For example, the IR spectrum of compound **7a** showed absorption bands at 3243 (NH_2), 3164 (NH), 2211 (CN), 1668 (C=N), 1617 (C=C) and 1044 cm^{-1} (C-O-C). Its ^1H NMR spectrum (DMSO-d_6) revealed signals at 9.0 (s, 1H, NH, exchangeable with D_2O), 8.1 (s, 1H, H-2 indole), 7.5–7.9 (m, 4H, Ar-H), 6.9 and 3.8 ppm (2s, 4H, $2NH_2$ exchangeable with D_2O). Its mass spectrum showed the molecular ion peak at *m/z* = 290 (2 %) and a base peak at *m/z* = 142.

Biological activity

The newly synthesized compounds were evaluated for their anti-inflammatory activity against carrageenean-induced rat's paw oedema by administration of 20 and 5 mg kg^{-1} (*p.o.*) using flufenamic acid (20 mg kg^{-1}) and indomethacin (5 mg kg^{-1}) as reference drugs. The data obtained (Table III) revealed that paw oedema was inhibited by oral administration of most test compounds at a dose level of 20 mg kg^{-1}. The most active test compounds were in the descending order of **6b**, **6g** > **3c**, **4e** > **4d**, **7e** > **2a**, **4b**, **4g** > **2e**, **7d** > **3d**, **3e**, **7g** > **4f**, **6a** > **6e** with inhibition effects ranging from 50 to 32 % compared to

Table IV. Anti-inflammatory activity of compounds in p*-benzoquinone induced writhing response in mice*

Compd. No.	Dose (mg kg^{-1})	Inhibition (%)	Compd. No.	Dose (mg kg^{-1})	Inhibition (%)
2d	20	50	**4g**	20	66
	5	16		5	16
2e	20	66	**6d**	20	42
	5	33		5	16
3b	20	50	**6e**	20	42
	5	16		5	33
3d	20	66	**6g**	20	66
	5	33		5	33
3e	20	42	**7d**	20	66
	5	33		5	16
3g	20	50	**7e**	20	42
	5	33		5	16
4c	20	16	**7g**	20	66
	5	0		5	16
4d	20	33	Negative control[a]	0	0
	5	16			
4e	20	42	Flufenamic acid	20	83
	5	16			
4f	20	50	Indomethacin	5	66
	5	16			

[a] 2 % Tween 80 is a negative control, also solvent for tested compounds and reference drugs.

flufenamic acid (53 %) at a dose of 20 mg kg^{-1} and indomethacin (51 %) at a dose of 5 mg kg^{-1}. The presence of aminopyrazole at position 3 of indole as in compounds **6b** and **6g** showed inhibition (50 %) dose to that of flufenamic acid (53 %) and indomethacin (51 %). Only, compounds **6a**, **6e**, **4e** and **4g** exhibited inhibition effects of 39, 39, 33 and 32 % at a dose of 5 mg kg^{-1} compared to indomethacin (51 %) at a dose of 5 mg kg^{-1}.

Analgesic activity of the synthesized compounds was studied using a *p*-benzoquinone induced writhing response in mice. The obtained data (Table IV) indicated that compounds **2e**, **3d**, **4g**, **6g**, **7d** and **7g**, at a dose of 20 mg kg^{-1}, showed the same equipotent writhing inhibition of 66 % as indomethacin at a dose of 5 mg kg^{-1}. On the other hand, the most active test compounds were in the descending order of **2e**, **3d**, **4g**, **6g**, **7d**, **7g** > **2d**, **3b**, **3g**, **4f** > **3e**, **4e**, **6d**, **6e**, **7e** with writhing inhibition of 66, 50 and 42 % compared to flufenamic acid (83 %) at a dose of 20 mg kg^{-1}. From the data obtained writhing inhibitions of the newly synthesized compounds seem to relate with the presence of halo atoms in these compounds.

Anticonvulsant properties of the tested compounds were studied using the electric shock seizure test. Data obtained (Table V) revealed that compounds **2d**, **2e**, **3d**, **4c**, **4f**, **4g**, **6a** and **6d**, at a dose level of 25 mg kg^{-1}, showed anticonvulsant protection (50 %) as did the reference drug diazepam at 5 mg kg^{-1}, while compounds **3b**, **3e**, **4d**, **6e**, **7d** and **7e**, at

Table V. Anticonvulsant activity of the most anti-inflammatory active compounds

Compd. No.	Dose (mg kg^{-1})	Inhibition (%)	Compd. No.	Dose (mg kg^{-1})	Inhibition (%)
2d	25	50	**4g**	25	50
	12.5	16		12.5	16
2e	25	50	**6a**	25	50
	12.5	33		12.5	33
3b	25	66	**6d**	25	50
	12.5	33		12.5	16
3d	25	50	**6e**	25	66
	12.5	33		12.5	33
3e	25	66	**6g**	25	33
	12.5	33		12.5	16
3g	25	33	**7d**	25	66
	12.5	16		12.5	16
4c	25	50	**7e**	25	66
	12.5	16		12.5	16
4d	25	83	**7g**	25	33
	12.5	50		12.5	16
4e	25	100	Negative control[a]	0	0
	12.5	66			
4f	25	50	Diazepam[a]	5	50
	12.5	16			

[a] 2 % Tween 80 is a negative control, also solvent for tested compounds and diazepam.

Table VI. Antimicrobial activity of the synthesized compounds

Compd No.	Inhibition zone (mm)									
	E. coli		*P. aeruginosa*		*S. aureus*		*B. cereus*		*C. albicans*	
	Compounds (μg per disc)									
	100	50	100	50	100	50	100	50	100	50
2a	13	10	15	11	11	8	10	7	13	9
2b	14	10	17	9	10	8	10	7	14	8
2c	15	8	19	10	10	8	10	7	13	8
2d	16	10	15	10	10	7	11	8	13	8
2e	17	10	14	10	10	7	11	8	13	8
2f	20	15	20	13	11	8	11	8	15	12
2g	20	14	20	13	12	8	11	8	14	12
3a	13	10	15	8	11	8	10	8	12	8
3b	12	10	16	8	10	8	10	8	11	8
3c	14	10	17	8	10	8	10	8	13	8
3d	15	10	13	10	11	8	10	8	14	8
3e	16	11	14	11	11	8	10	8	13	8
3f	14	8	13	8	11	8	11	8	13	11
3g	14	8	13	8	11	8	11	8	13	8
4a	12	–	14	8	10	8	11	8	11	8
4b	12	–	14	8	10	8	11	7	11	8
4c	13	8	19	–	10	8	11	8	10	8
4d	11	–	19	–	10	8	11	7	10	–
4e	10	–	19	–	10	8	11	7	10	–
4f	14	9	12	8	11	8	11	8	13	11
4g	14	9	12	8	12	8	11	7	14	11
6a	12	8	13	8	10	8	10	8	12	9
6b	12	8	13	8	9	7	11	8	11	8
6c	17	8	13	9	11	–	12	–	11	8
6d	18	8	17	8	10	–	10	–	11	8
6e	16	8	19	8	11	–	11	–	11	8
6f	20	14	19	14	11	–	10	–	12	8
6g	20	14	19	14	10	–	12	–	11	8
7a	14	9	19	10	10	–	11	–	11	8
7b	14	9	17	10	10	–	10	–	12	8
7c	15	7	18	10	10	–	10	–	14	8
7d	14	8	19	10	10	–	10	–	12	8
7e	13	8	20	10	10	–	10	–	11	8
7f	17	11	12	8	10	–	10	–	11	8

Table VI. continued

7g	17	10	12	8	10	–	10	–	11	8
Cefatoxime (30 μg per disc)	32	22	22	18	31	26	26	20	–	–
Piperacillin (100 μg per disc)	–	–	20	15	27	18	20	15	–	–
Nystatin (30 unit per disc)	–	–	–	–	–	–	–	–	40	

a dose level of 25 mg kg^{-1} exhibited even higher protection (66 to 83 %) than diazepam at 5 mg kg^{-1}. Compound **4e**, at dose levels of 25 and 12.5 mg kg^{-1}, was found to be the most potent compound as it induced 100 and 66 % protection whereas diazepam (5 mg kg^{-1}) caused only 50 % protection against convulsion. It is clear that pyrano(2,3-*c*) pyrazole compounds **4e** and **4d** with no chlorine atoms showed higher activity than that with chlorine atoms. Meanwhile, compound **4e** (with the chlorine atom at *o*-position) showed higher protection (100 %) than **4d** with chlorine at *p*-position (83 %).

All the newly synthesized compounds were tested for their antimicrobial activity at different doses of test compounds (Table VI). Compounds **2f**, **2g**, **6f** and **6g**, at 100 μg per disc, were found to be the most active of all test compounds with an inhibition zone of 20 mm against *E. coli* compared to the reference drug cefatoxime (32 mm) at 30 μg per disc and their activity may be associated with the presence of pyrazole moiety at position 3 of indole and existence of the chlorine atom. Compounds **2f**, **2g**, **3b**, **3c**, **4c**, **4d**, **4e**, **6d**, **6e**, **6f**, **6g** and **7a** which contain pyrazole or pyramo(2,3-*c*)pyranole at position of indole showed potent activity only towards *P. aeruginosa* with the inhibition zone ranging from 17 to 20 mm compared to cefatoxime (22 mm) at 30 μg per disc and piperacillin (20 mm) at 100 μg per disc. All the test compounds showed slight to moderate activity towards Gram-positive bacteria at 100 μg per disc compared to the reference drug piperacillin.

CONCLUSIONS

A series of new 3-[(*N*-substituted indol-3-yl)methyleneamino]-6-amino-4-aryl-pyrano(2,3-*c*)pyrazole-5-carbonitriles (**3a**-**g**, **4a**-**g**) and 3,6-diamino-4-(*N*-substituted-indol-3-yl) pyrano(2,3-*c*)pyrazole-5-carbonitriles (**7a**-**g**) have been synthesized and tested for their anti-inflammatory, analgesic, anticonvulsant and antimicrobial activities. Depending on the obtained results, the newly synthesized compounds with pyrano(2,3-*c*)pyrazole nucleus at 3-position of indole moiety show anti-inflammatory, analgesic and anticonvulsant activities which are increased by the presence of halo atoms. The anticonvulsant potency of certain tested compounds was more pronounced than both the anti-inflammatory and analgesic activities. Moreover, most of the newly synthesized compounds showed potential antimicrobial activity.

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SAŽETAK

Sinteza i potencijalno biološko djelovanje novih 3-((*N*-supstituiranih indol-3-il)metilenamino)-6-amino-4-aril-pirano(2,3-*c*)pirazol-5-karbonitrila i 3,6-diamino-4-(*N*-supstituiranih indol-3-il)pirano(2,3-*c*)pirazol-5-karbonitrila

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U radu se opisuje sinteza novih 3-[*N*-supstituiranih indol-3-il)metilenamino]6-amino--4-aril-pirano(2,3-*c*) pirazol-5-karbonitrila (**3a-g** i **4a-g**) kiselo-kataliziranom kondenzacijom *N*-supstituiranih indol-3-karboksaldehida (**1a-g**) s 3-amino-5-pirazolonom iza koje slijedi reakcija s ariliden malononitrilom. Serija novih 3,6-diamino-4-(*N*-supstituiranih indol-3-il)pirano(2,3-*c*)pirazol-5-karbonitrila (**7a-g**) sintetizirana je reakcijom malononitrila s produktima **6a-g**, koji su pripravljeni bazno-kataliziranom kondenzacijom **1a-g** s 3-amino-5-pirazolonom. Neki spojevi iz serije **7a-g** dobiveni su reakcijom *N*-supstituiranih 3-indolidin malononitrila (**5a-g**) s 3-amino-5-pirazolonom. Novosintetizirani spojevi imaju značajno protuupalno, analgetsko i antikonvulzivno djelovanje. Antikonvulzivno djelovanje pojedinih testiranih spojeva bilo je jače izraženo nego protuupalno i analgetsko djelovanje. Većina ispitivanih spojeva pokazuje antimikrobno djelovanje na *Escherichia coli* i *Pseudomonas aeruginosa*.

Ključne riječi: indol, pirano(2,3-*c*)pirazol, protuupalno, analgetsko, antikonvulzivno, antimikrobno djelovanje

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