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Structural studies on nitroimidazooxazoles with antitubercular and antileishmanial activities

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2,3-Dihydro-2-ethyl-6-nitroimidazo[2,1-b]oxazole and 2,3-dihydro-3-phenyl-6- nitroimidazo[2,1-b]oxazole are found to exhibit good *in vitro* and *in vivo* activity against *Leishmania donovani*. These molecules had been reported earlier to have potent antitubercular properties. Since the synthetic route to these involves opening mono substituted oxiranes by 2,4-dinitroimidazole, many structural possibilities exist for the products, particularly regarding location of the substituent (ethyl, phenyl) in the oxazole ring. The structures given earlier by us needed confirmation. Single crystal X-ray studies have confirmed the structure of the product from butylene oxide and has led to revision of structure of the product from styrene oxide. NMR spectra, HMBC spectrum and proton coupled ^{13}C NMR spectrum of the monocyclic precursor alcohols have established their structures convincingly.

Keywords: Nitroimidazoles, 2,3-dihydro-2-ethyl-6-nitroimidazo[2,1-b]oxazole, 2,3-dihydro-3-phenyl-6-nitroimidazo[2,1-b]oxazole, HMBC spectrum, NOESY spectrum, single crystal X-ray study

Nitroimidazoles are a class of anti-bacterial agents which hold great potential to address major unmet medical needs in clinical practice. Nitroheterocyclic compounds, including various 5-and 2-nitroimidazoles are known to be effective against a variety of protozoan and bacterial infections in humans and animals[1-4] but there were few reports until recently of members of this class having activity against tuberculosis, a dreaded human disease[5]. In an extended program for developing antiprotozoal nitroimidazoles culminating in the discovery of satranidazole[6], Nagarajan *et al*. synthesized besides a large number of monocyclic compounds, a limited library of nitroimidazooxazoles exhibiting wide spectrum anti-TB activity among which CGI17341, **1** was the most potent and had a desired spectrum but was found to be mutagenic[7,8].

However, gratifyingly it inspired efforts from other centers of research which culminated in the discovery and development of delamanid[9] **4**, an analogue of **1** which is registered in Europe and a homologue, PA 824, a nitroimidazooxazine[10] **5** which is in advanced clinical trials and another analogue, TBA-354[11], which is slated to enter the clinic.

Through the courtesy of DNDi, a selection of mono and bicyclic nitroimidazoles, including nitroimidazooxazoles which had been synthesized during our work on satranidazole[6] were evaluated for potential antileishmanial activity during 2005 and 2006. A few mono and bicyclic nitroimidazoles were found to be of interest. Among these the nitroimidazooxazole **1** and the phenyl analogue **2** previously formulated as **3** were found to have potent activity *in vitro* against axenic culture and in the macrophage and had high safety indices[12], being better in all the parameters compared to standards. They had good *in vivo* activity also in the hamster model by the i.p. route and DNDi had proposed to study the activity by the oral route but Ames and Micronucleus Assay tests commissioned by them in 2007 revealed them to be genotoxic. The mutagenicity of **1** had been already reported by one of

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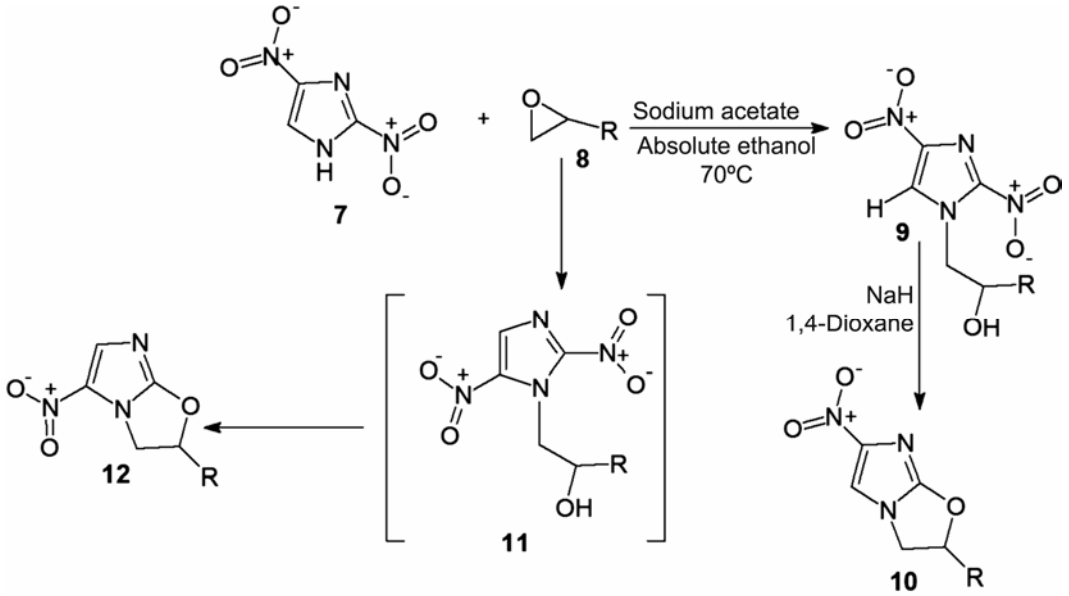
us[7]. However DNDi informed us that this structural motif for a nonmutagenic candidate may be a fruitful approach to synthesize a right candidate in the class of nitroimidazooxazoles. Collaboration of DNDi with the Global Alliance for TB beginning July 2010 gave them access to a number of nitroimidazooxazines like PA 824 **5** and their ring contracted analogues, nitroimidazooxazoles of the type CGI17341, **1** and delamanid **4** which were diligently tested in antileishmanial screens. This has culminated in identifying DNDi-VL-2098 **6** as a highly active, nonmutagenic candidate for preclinical studies[13,14] after the publication of our paper[12].

The demonstration of good anti-TB activity and potentially useful antileishmanial activity for the prototypes **1** and **2**, the growing list of publications in nitrobicyclic imidazoles in TB therapy and the innate complexity of the chemistry involved in their synthesis (reaction of 2,4-dinitroimidazole with oxiranes, **Scheme** I) prompted a re-examination of the structures of the two compounds. Hence detailed NMR and single crystal X-ray studies were undertaken on **1** and **2** to place their structures beyond doubt and aid researchers who may be using the oxirane route for similar molecules[15,16].

Results and Discussion

The nitroimidazooxazoles were re-synthesized as reported in the literature[7] by the reaction of 2,4-dinitroimidazole **7** with substituted oxiranes **8** which has been shown to occur as in Scheme I. The preferred attack by **7** at the less substituted carbon atom of oxiranes **8** has been proposed earlier[17]. The reaction is complex under the conditions described and usually gives rise to three identifiable products - 6-nitroimidazooxazole **10**, their 5-nitro isomers **12** and the open chain 2,4-dinitroimidazolyl alcohols **9**. In such reactions **10** is formed from **9** by elimination of nitrous acid. Alcohols **11** isomeric with **9** were evidently formed but were totally converted to the cyclic products **12** during the reaction. The 2,4-dinitroimidazolyl ethanols **9** underwent cyclization in the presence of sodium hydride or sodium acetate to afford bicyclic products **10** in moderate to high yields. The location of the nitro group in **1** and **2** [earlier formulated as **3**] was deduced from solvent induced chemical shifts in their ^{1}H NMR spectra[18]. However, the assignment of moiety R to position 2 in **1** and the phenyl analogue CGI17283 was dictated solely by the assumption that the NH [in **7**, one tautomeric form] would attack the less substituted carbon atom in oxiranes **8** as depicted in the Scheme I. The resulting alcohols, **14** and **15** will cyclize to **1** and **3** respectively. On the other hand, the consequence of attack by **7** on **8** at the more substituted carbon will be alcohols **13** and **16** which will cyclise to **17** and **2** respectively. Literature precedent exists to show that styrene oxide also gets partially opened by nucleo-philes at the benzylic carbon atom[19]. Hence we undertook a detailed study of the ^{1}H NMR correlation spectra of these molecules to secure confirmatory evidence for **1** and **2**. It has to be noted that the reaction can again give the 5-nitro isomers of the alcohols and the corresponding cyclic products.



Scheme I

NMR spectral correlation studies on 1 and 2

The ^{1}H and ^{13}C NMR spectral data of 2-ethyl-6-nitro-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole **1** and 6-nitro-3-phenyl-2,3-dihydroimidazo[2,1-*b*][1,3]oxazole **2** have been communicated[12] in brief.

In the HMBC spectrum of **1** the signal due to C5 which was readily located at δ 116.5 due to the strong one bond coupling with the attached proton (signal at δ 7.53, s) showed no correlation with the signals of the protons on C3 (3.94, 4.37) or C2 (5.27). Hence the correlation spectrum was unhelpful in choosing between **1** and **17**.

In the HMBC spectrum of **2**, C5 was located at δ 115.6, identified by the strong one bond coupling with the attached proton (singlet at δ 7.42). This signal again showed no correlation with the signals due to the protons on C3 and C2 at δ 4.84, 5.36 and 5.8. Thus we were unable to assign structure **2** or **3** from the HMBC spectrum.

Further, in the proton coupled spectrum, the signal of C5 was only seen as a large doublet with no further fine splitting with C2 or C3 proton.

Thus we were unable to make an unequivocal structural assignment to the bicyclic molecules **1** and **2** based on NMR studies, but could do it by X-ray single crystal studies (*vide infra*). However we felt that the lack of HMBC correlation may be inherent to such bicyclic systems which we had also encountered in our earlier work[18]. The alcohol precursors **13** or **14** and **15** or **16** do not suffer from this handicap and we felt a solution could be possible through a study of their NMR spectra.

1-(2,4-Dinitro-1*H*-imidazol-1-yl)butan-2-ol, 14

The ^{1}H NMR spectrum in DMSO-d_6 showed the following peaks.

H (5) 8.71 (1H, s), OH 5.13 (1H, d, J = 5.0Hz), H (6) 4.60 (1H, m), H (6) 4.25 (1H, m), H(7) 3.73(1H, bs), H (8) 1.50 (1H, m), H (8) 1.40(1H, m), H (9) 0.932 (3H, t J = 7.5Hz).

The interconnectivity of proton signals was made by study of the COSY spectrum. The solvent induced differential shifts of the ring protons in $CDCl_3$ and DMSO-d_6 helped us to establish that the proton at δ 8.71 was located on C-5. Importantly, the hydroxyl proton signal seen as a doublet (J = 5.0 Hz) at δ 5.13 was clearly coupled to H (7) indicating that it was a secondary alcohol leading to **14** as the unique structure. In the NOESY spectrum, proton at C-5 had a NOE effect on the signals due to the C-6 proton at 4.6 and 4.3 confirming that the CH_2 group was attached to nitrogen (N1). The ^{13}C NMR spectrum had the following peaks

C (2) 142.40, C (4) 142.29, C (5) 127.37, C (7) 70.14, C (6) 56.31, C (8) 27.61, C (9) 10.17.

Connectivity of individual carbon atoms and protons was shown by study of ^{13}C-HSQC spectra:

C-5 127.37 H-5 8.71

C-6 56.31 H-6(2 protons) 4.60, 4.25

C-7 70.14 H-7 3.73

Carbon atoms at δ 142.40 and δ 142.29 carried no protons. The proton doublet at δ 5.13 not attached to any carbon atom was clearly due to the hydroxyl group.

In the HMBC spectrum, the signal for C-5 at δ 127.4 was easily identified by the coupling with proton at δ 8.71(H-5). This carbon signal also correlates with the CH_2 protons at δ 4.60 and δ 4.25 (H-6), thus simultaneously confirming that C-5 is unsubstituted and that C-4 carries the NO_2 group. The structure of the alcohol is thus confirmed to be **14** and the resulting cyclic product is indeed **1**.

2-(2,4-Dinitro-1*H*-imidazol-1-yl)-2-phenylethanol, 16

The ^{1}H NMR spectrum in DMSO-d_6 showed the following peaks.

H (5) 9.00(1H, s), H (2^1, 3^1, 4^1, 5^1, 6^1) 7.40 (5H, m), H (6) 6.23 (1H, dd), OH 5.45 (1H, s), H (7) 4.26 (1H, dd), H (7) 4.07 (1H, dd).

The lower field chemical shift (in DMSO-d_6) of the ring proton (δ 9.00) relative to its position in $CDCl_3$ (δ 8.22) allowed us to locate it on C5 and the nitro group on C4. The high field protons were assigned by HSQC studies in the present assignment (See below).

The ^{13}C NMR spectrum had the following peaks

C (2)-143.40, C (4)-142.20, C (1^1)-135.96, C (6^1 & 2^1)-129.27, C(4^1)-129.08, C(3^1 & 5^1)-127.79, C (5)-124.87, C (6)-66.12, C (7)-63.12.

HSQC correlations

C (5) 124.87 H (5) 9.00

C (6) 66.12 H (6) 6.23

C (7) 63.12 H (7) 4.26, 4.07

In the HMBC spectrum, C-5 showed clear correlation with H-6, as also C-2^1 and C-6^1 with C-6 H. Further in the ^{1}H-^{13}C coupled spectrum, C-5 was split into a large doublet by H-5 and further into fine doublets by H-6(J = 205 Hz, 5 Hz) (and not triplets) which would be required by structure **16**. Thus these data confirm unequivocally the structure of the alcohol to be **16** and not **15**. Consequently, the cyclised product has to be **2**.

Interestingly the R and S enantiomers of structure **3** were reported in 2012 (Ref 20) much later to our

original publication in 1989 (Ref 7). These were synthesized by the oxirane (R and S styrene oxides) but used 2-chloro-4(5)-nitroimidazole whereas 2,4-dinitroimidazole and RS-styrene oxide were our reagents. The reported ^{1}H NMR data for R3 (=S3) are different from ours. The same was the case for the data for the alcohol **15** (R and S) in $CDCl_3$ compared to our findings for **16**. The authors has also prepared R and S enantiomers of **1**, using butylene oxide and 2,4(5)-dinitroimidazole and the ^{1}H NMR data of the enantiomers are identical to our data for **1** as expected. This paper has not cited our work. It is quite possible that in our hands, in the complex mixture of products from the reaction of 2, 4(5)-dinitroimidazole with RS-styrene oxide, RS **3** may have been present but had evaded isolation.

These results also suggest that 2-nitro-, 2-chloro- and 2-bromo- (also used by some researchers[14]) -4-nitroimidazoles commonly used for synthesis of nitroimidazooxazoles and oxiranes under similar conditions may lead to mixtures of different compositions. This merits detailed investigations.

Thus we have demonstrated successfully the use of NMR correlation spectra for structure assignment of alcohols arising from the opening of oxiranes with 2,4-dinitroimidazoles and as a corollary, structure assignments of their cyclized products. More significantly in the absence of X-ray studies; our NMR techniques should be helpful in assigning structures to newer anti-TB and anti-leishmanial molecules incorporating the nitroimidazooxazole scaffold.

Single Crystal X-ray Study

Single crystal X-ray studies confirmed the structure of **1** (C_2H_5 group on C-2) while they revealed that the phenyl group had to be located on C-3 as in **2** and not on C-2 as in **3** as postulated earlier.

Crystallization

Compound **1** was crystallized from a 1:1 mixture of ethyl acetate and THF by slow evaporation while **2** was crystallized from acetonitrile solvent.

Single crystal X-ray diffraction and crystal structure refinement

Single crystal X-ray diffraction data were collected on an Oxford Xcalibur Eos (Mova) Diffractometer using MoKα radiation (λ = 0.7107 Å) with X-ray generator operating at 50 kV and 1 mA at 100 K temperature[21]. The structures were solved and refinement was carried out using SHELX97 (Ref 22) module in the program suite WinGX[23].The geometric calculations were carried out by PARST95 and PLATON[23]. Molecular diagrams were generated using ORTEP-3 (Ref 21) and the packing diagrams were generated using Mercury 2.3.

Crystallographic refinement details are given in Table I and relevant intermolecular interactions in supplementary data. The ORTEPs are shown in Figure 1.

Compound **1** crystallizes in space group $P2_1$ space group with Z = 4. Since the molecule lacks classical hydrogen bond donor groups, the crystal packing is stabilized by C–H···O interactions predominantly (Table II). The oxygen atom O2 on the nitro functional group acts as an acceptor to a bifurcated C–H···O hydrogen bond. The ability of multifurcated C–H···O hydrogen bonds to support crystal packing has been quantitatively demonstrated. The crystal contains a racemic mixture of R and S forms (chiral centre being atom C-5), with opposite enantiomeric forms packed in an overlapping manner. This results in a crystallo-

Table I — Crystallographic refinement details

Data	**1**	**2**
Formula	$C_{11}H_9N_3O_3$	$C_7H_9N_3O_3$
Formula weight	231.21	183.17
CCDC number	900927	900926
Temperature (K)	100 K	100 K
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1$
a (Å)	13.1083(3)	5.5702(3)
b (Å)	5.6434(1)	6.3387(3)
c (Å)	14.1795(3)	11.7930(5)
α (°)	90	90
β (°)	102.243(2)	101.667(5)
γ (°)	90	90
Volume (Å^3)	1025.08(4)	407.78(3)
Z	4	4
Density (gcm^{-3})	1.498	1.492
μ (mm^{-1})	0.113	0.119
F (000)	480	192
$h_{min, max}$	−16,16	−6,6
$k_{min, max}$	−6, 6	−7, 7
$l_{min, max}$	−17,17	−14, 14
No. of unique reflections	2007	1554
No. of parameters	154	137
$R_{\_all}$, $R_{\_obs}$	0.0428, 0.0380	0.0438, 0.0380, 0.0525
$wR2_{\_all}$, $wR2_{\_obs}$	0.1004, 0.0963	0.0973, 0.0926
$\Delta\rho_{min,max}$ (e Å^{-3})	−0.286, 0.238	−0.267, 0.168
GOOF	1.105	1.049

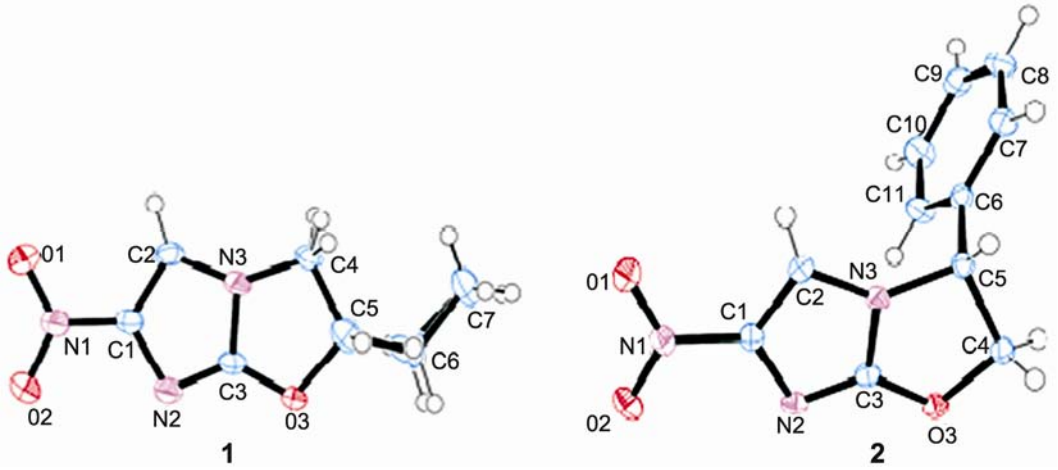


Figure 1 — ORTEP of **1** and **2** plotted with 50% probability ellipsoids and the relevant atom numbering scheme

Table II — Relevant intermolecular interactions

	D-H···A	D-H/Å	D···A/Å	H···A/Å	∠D-H···A/°	symmetry
1	C2 –H2···O2	0.93	3.310(2)	2.38	175	x+1,+y,+z
	C4 –H4ab···O1	0.97	3.563(7)	2.59	178	x+1,+y,+z
	C4–H4bd···O3	0.97	3.216(2)	2.61	121	x+1,+y,+z
	C4–H4aa···O3	0.97	3.216(2)	2.61	121	x+1,+y,+z
	C4–H4bc···O1	0.97	3.583(7)	2.61	177	-x+1,+y+ ½,-z
	C4–H4ab···O1	0.97	3.565(7)	2.60	178	-x+1,+y- 1/2,-z
	C5a –H5a···O2	0.98	3.119(1)	2.39	131	-x,+y+ 1/2,-z
2	C2–H2···N2	0.93	3.417(2)	2.61	146	x,+y+1,+z
	C5–H5···O3	0.98	3.390(2)	2.60	138	x,+y+1,+z
	C4–H4a···O2	0.97	3.196(2)	2.61	119	x+ ½,-y- ½, +z+ ½

graphic disorder, involving atoms C-4, C-5, C-6 and C-7 along with their attached hydrogen atoms. The ethyl group connected to chiral carbon atom C-5 thus gets distributed in opposite directions (Figure 2). This static positional disorder has been treated during the crystal structure refinement using PART command in SHELX with 0.5 occupancy for individual carbon atoms and connected hydrogen atoms in the ethyl group.

As it is commonly observed in case of racemic crystal structures, the compound **2** crystallizes in a centrosymmetric space group with one of the enantiomers in the asymmetric unit (space group $P2_1/n$, Z = 4). The asymmetric unit has no disordered atom, unlike in case of **1**. The ORTEP representing one of the enantiomeric forms is shown in Figure 1. The molecules are packed by means of C–H···N and C–H···O interactions (Table II). The oxygen atom O1 in nitro group acts as a bifurcated acceptor to C–H···O hydrogen bonds.

It is a general trend that enantiomeric pure compunds crystallize in chiral space groups and the corresponding racemic mixtures adopt centrsosymmetric

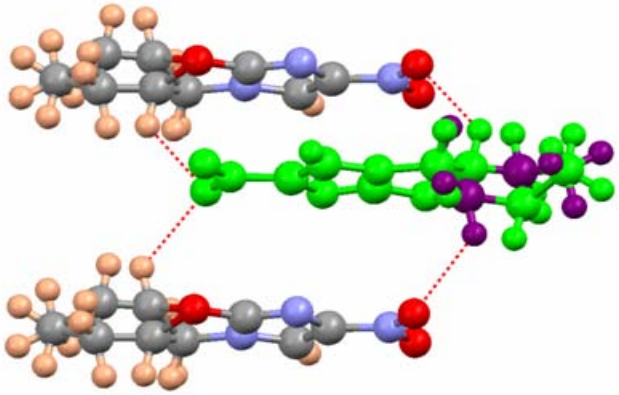


Figure 2 — Crystal packing in **1** supported by C–H···O hydrogen bonds (only one of the disordered ethyl positions has been shown, for clarity)

space groups (in such a way that the enantiomeric pairs are related by a cenre of symmetry). However, the crystal packing of **1** represents a rather unusual case of a racemate crystal adopting chiral space group. Interestingly, the static crystalline disorder

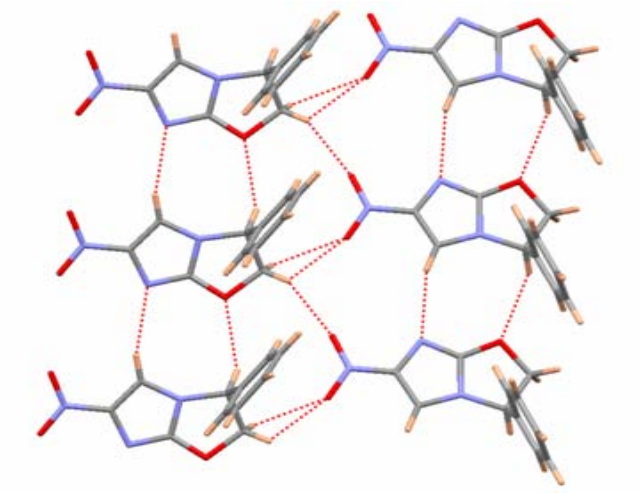


Figure 3 — Crystal packing in **2** supported by C–H···O and C–H···N hydrogen bonds

facilitates the packing of racemates in a chiral fashion (this is contrary to the common observation that the crystallographic disorder results in an increase in symmetry- especially in order-diosrder transitions). It is to be noted that in the crystal structure of **1**, the molecules stack in such a way that it facilitates similar C–H···O hydrogen bonds on either sides of the molecule (Figure 3). The nitro groups of the neighbouring molecules positioned on either side act as the hydrogen bond acceptors. Thus, it offers the possibility of packing the enantiomeric pairs in an overlapping fashion. On the other hand in case of **2**, the phenyl group causes steric hinderence denying such a stacked molecular arrangement.

Hirshfeld surface analysis

Hirshfeld surface analysis was carried out for a quantitative understanding of the varying levels of contribution from the weak intermolecular interactions such as C-H···O and C-H···N hydrogen bonds present in **1** and **2** (Figure 4). Since the crystal structure of **1** has disorder, only half of the disordered positions of atoms in ethyl group were considered for the calculation of Hirshfeld surface. The Hirshfeld fingerprint analysis shows that C-H···O hydrogen bonds contribute the major proportion (41.7% in **1** and 32.9% in **2**) to the intermolecular interactions and π···π stacking is absent in both **1** and **2**. The contribution of C-H···N hydrogen bonds is also significant (10.6% in **1** and 12.1% in **2**). The relative contribution of various intermolecular interactions are given in Figure 5.

Further, based on the obtained crystal geometry, electrostatic potential (esp) surfaces were calculated

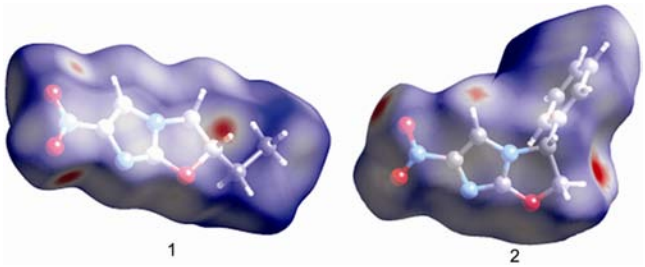


Figure 4 — Hirshfeld d_{norm} surfaces of **1** and **2** highlighting the intermolecular interactions

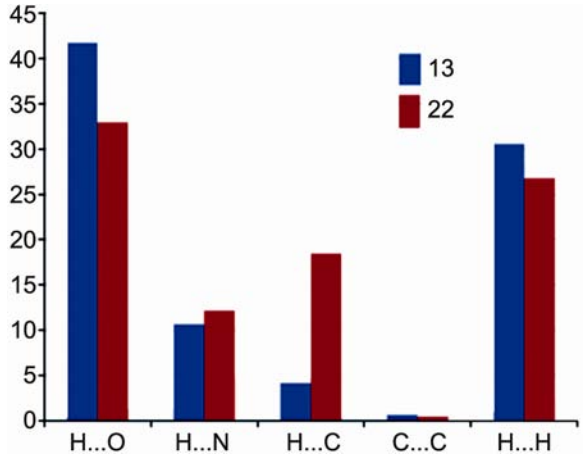


Figure 5 — Proportions of intermolecular interactions in **1** and **2** obtained from Hirshfeld finger print analysis

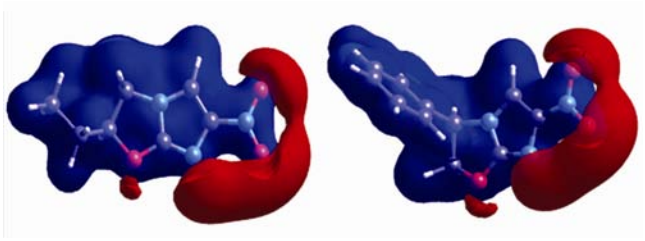


Figure 6 — Electrostatic potential (esp) surfaces for **1** and **2** (isovalue 0.05 0.05 e/au^3)

and plotted over the observed molecular conformations of **1** and **2** (Figure 6). The calculations were carried out using TONTO interface in Crystal Explorer and esp surfaces were generated for an isovalue of 0.05 e/au^3.The esp plots indicate the possible binding modes of these molecules in their active sites. In the present case similarity in the esp plots suggests similar activity profiles for **1** and **2**.

Experimental Section

The melting points of the compounds are recorded by open capillary method and are uncorrected. ^{1}H NMR spectra are recorded (in DMSO-d_6/$CDCl_3$) on a 400/500 MHz NMR spectrometer using TMS as

internal standard. The mass spectra were recorded on BUCHI B-540 spectrometer operating at 70 eV.

Conclusion

Nitroimidazooxazoles **1** (CGI17341) and **2** have important biological activities. Compound **1** has pronounced anti-TB activity while **1** and **2** have been later found to have significant antileishmanial properties establishing them to be important leads for potential drugs in this area. Our synthesis leading to **1** and **2** could give rise to several isomers and hence we attempted to develop unambiguous methods for a solution. Since HMBC spectra did not provide an answer for the bicyclic molecules, we looked at their precursor alcohols where HMBC and NOESY spectra gave clear answers to their architecture. Structure **14** earlier assigned for the alcohol from butylene oxide was confirmed and hence **1** which arose from cyclization of **11**. In the case of the alcohol from styrene oxide, the present NMR studies ruled out the structure **15** assigned earlier and established **16** as the right one. As a result, the structure of the bicyclic nitroimidazooxazole obtained from **16** had to be revised as **2**. Single crystal X-ray studies carried out simultaneously confirmed the above structural assignments. We believe that the NMR studies disclosed in this paper will be very useful for all researchers engaged in synthesis and study of nitroimidazooxazoles. It is emphasized that this exercise is non-trivial considering that the reaction of 2,4-dinitroimidazole (also the 2-haloanalogues) with substituted oxiranes can in principle give eight different alcohols which in turn can cyclize to eight different nitroimidazooxazoles.

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