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Synthesis and anti-tuberculosis studies of 10-phenyl sulfonyl-2-alkyl/aryl- 4, 10 dihydrobenzo [4, 5] imidazo [1, 2-a] pyrimidin-4-one derivatives

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A series of novel 10-phenylsulfonyl-2-substituted-4,10 dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-4-one derivatives obtained from N-sulfonation of 2-substituted-pyrimido[1,2-a]benzimidazol-4(10H)-ones and screened for for their in vitro anti-tuberculosis activities against Mycobacterium tuberculosis H37Rv by Microplate Alamar Blue Assay (MABA) method. The structures were established on the basis of their IR, ^{1}H-NMR, ^{13}C-NMR, ESI-MS data and also the compound with **3f** were crystallized and analysed by single crystal X-ray diffraction studies.

1. Introduction

Tuberculosis (TB) is a dangerous disease caused by species found in Mycobacterium tuberculosis complex that includes M. tuberculosis (Mtb). In the year 2012, an estimated 8.6 million people developed TB and 1.3 million died from the disease[1] (including 320 000 deaths among HIV-positive people). The number of TB deaths is unacceptably large given that most are preventable. Nearly 20 years after the WHO declaration of TB as a global public health emergency. So the novel therapeutics is necessary to treat both drug- susceptible TB and progressively common drug resistant strains.

Pyrimido [1,2-a] benzimidazoles were the class of fused cyclic bridgehead nitrogen compounds represent a pharmaceutically important class of compound because of their diverse range of biological activities as antineoplastic,[2] anti-tumor,[3] cytotoxic agents,[4,5] antiulcer and imunotropic compounds.[6,7] Coumarin substituted dihydrobenzo[4,5]imidazo[1,2-a]pyrimidin-4-one was found to be the most potent cytotoxic compound (88%) against Dalton's Ascitic Lymphoma cell,[8] 1-[(2E)-3-phenylprop-2-enoyl]-1H-benzimidazole was found to be anti-tubercular activity against Mycobacterium tuberculosis H37Rv.[9] As sulfonamides (SO_2–NH) have great importance in medicinal chemistry, with various biological activities such as HIV protease inhibitors,[10] anti-tumor,[11] carbonic anhydrase (CA) inhibitors,[12] anti-inflammatory,[13] anti-cancer activities,[14,15] antiviral,[16,17] antibiotics.[18] Recently shah et.al reviewed the medicinal chemistry of sulfonamide derivatives.[19]

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Considering the biological significance of nitrogen containing heterocycles like pyrimidones, sulphonamide moieties, we here designed and synthesised phenyl sulfonyl substituted pyrimido [1, 2-a] benzimidazolone derivatives (fig 1).

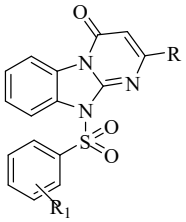
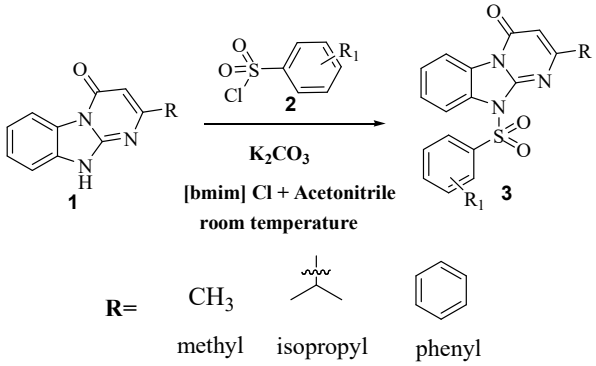


Fig. 1. Structure of target compound

2. Results and Discussion

As depicted in **Scheme 1**, the key intermediate 1 was prepared as reported [20] and 10-Phenyl sulfonyl-2-alkyl-4, 10 dihydrobenzo [4, 5] imidazo [1,2-a]pyrimidin-4-ones **(3a-3i)** were obtained by condensation of phenyl sulfonyl chloride (2) with pyrimido [1, 2-a] benzimidazolones (1a-1c) using K_2CO_3 as a mild catalyst in solvent (acetonitrile and [bmim]Cl) at room temperature for 18-24 min **(table 1)**. All the synthesized compounds 3a–3i was purified by recrystallization using ethanol solvent. The structures of target compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, ESI-MS techniques and single crystal.



R_1 = 3,4-dichloro, 2,5-dichloro, 2,5-dimethoxy.

Scheme 1. Synthesis of 10-Phenyl sulfonyl-2-alkyl-4, 10 dihydrobenzo [4, 5] imidazo [1,2-a]pyrimidin-4-ones **(3).**

Table 1. Synthesis of 10-Phenyl sulfonyl-2-alkyl/aryl-4, 10 dihydrobenzo [4, 5] imidazo [1,2-a]pyrimidin-4-ones **(3)**

Entry	1 (2R-Pyrimido [1, 2-a] benzimidazolones) R=	2 (R_1-Benzene Sulphonyl Chloride) R_1=	3	Time (min)	Yield (%)	MP (°C)
1	**Methyl**	3,4 Dichloro	**3a**	20	79	205-207
2	**Methyl**	2,5 Dichloro	**3b**	18	82	206-208
3	**Methyl**	2,5 Dimethoxy	**3c**	24	83	127-130
4	**Isopropyl**	3,4 Dichloro	**3d**	20	90	160-162
5	**Isopropyl**	2,5 Dichloro	**3e**	20	84	157-160
6	**Isopropyl**	2,5 Dimethoxy	**3f**	21	85	180-183
7	**Phenyl**	3,4 Dichloro	**3g**	20	80	189-192
8	**Phenyl**	2,5 Dichloro	**3h**	21	82	220-223
9	**Phenyl**	2,5 Dimethoxy	**3i**	23	83	217-220

The antituberculosis activity of all the newly synthesized compounds (3a-3i) was investigated against mycobacterium tuberculosis H37Rv strain by microplate alamar blue assay (MABA) method and the corresponding results are shown in **table 2**. As evident from the table, all the newly synthesized compounds exhibited anti-tubercular activity with moderate values, with a minimum inhibitory concentration (MIC) of 50.0 µg mL^{-1}. The MIC is defined as the lowest concentration (µg mL^{-1}) of the compound required to inhibit the bacterial growth, completely. All compounds showed moderate in vitro activity against H37Rv strain as compared to pyrazinamide and streptomycin (MIC = 3.12 and 6.25 µg mL^{-1}) respectively.

Table 2. Anti-tubercular activities and log P measurements of 10-Phenyl sulfonyl-2-alkyl/aryl-4, 10 dihydrobenzo [4, 5] imidazo [1,2-a]pyrimidin-4-one derivatives.

Compound	R_1	MIC µg mL^{-1}	Log *P* [a]
3a	3,4 Dichloro	50	4.027
3b	2,5 Dichloro	50	4.027
3c	2,5 Dimethoxy	50	2.784
3d	3,4 Dichloro	50	5.083
3e	2,5 Dichloro	50	5.083
3f	2,5 Dimethoxy	50	3.841
3g	3,4 Dichloro	50	5.478
3h	2,5 Dichloro	50	5.478
3i	2,5 Dimethoxy	50	4.235
Pyrazinamide	-	3.12	-0.71
Streptomycine	-	6.25	-5.35
Ciprofloxacin	-	3.12	-0.70

[a] Calculated by http://www.molinspiration.com/

Fig. 2 shows the ORTEP view of the molecule with atomic labeling and the displacement ellipsoids of non-hydrogen drawn at 50% probability level.

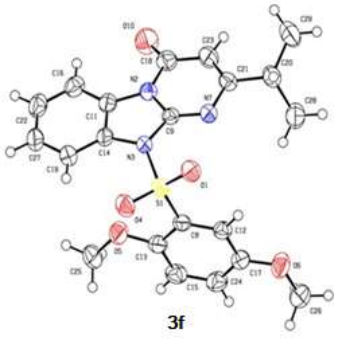


Fig. 2. The ORTEP diagram of the compound 3f showing the displacement ellipsoids of non-hydrogen atoms drawn at the 50% probability level

3. Conclusions

In summary, in order to develop the potent anti-tubercular agents, we developed the design and synthesis of 10-Phenyl sulfonyl-2-alkyl-4, 10 dihydrobenzo [4, 5] imidazo [1, 2-a] pyrimidin-4-ones (3) and evaluated for their in vitro anti-tuberculosis activities against Mycobacterium tuberculosis H37Rv by microplate alamar blue assay (MABA) method.

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4. Experimental

4.1. Materials and Methods

All solvents and reagents were commercial grade and used without further purification unless otherwise stated. Melting points were uncorrected. Nuclear magnetic resonance spectra were obtained on a Bruker AMX spectrophotometer in CDCI3 at 300 MHz. Chemical shifts were obtained in parts per million and were measured using tetramethylsilane (TMS) as reference. IR spectra were recorded on a Shimadzu FT-IR-8400S spectrophotometer using KBr pellets and are reported as wave numbers (cm^{-1}). Single Crystal X-ray analysis was done on Oxford Diffraction Xcalibur Eos Gemini diffractometer, complete crystal structure results as a CIF file including bond lengths, angles, and atomic coordinates are deposited in the Cambridge Crystallographic Data Center (CCDC).

4.2. Single crystal X-ray data collection.

CrysAlis PRO (Oxford Diffraction, 2009); cell refinement: CrysAlis PRO (Oxford Diffraction, 2009); data reduction: CrysAlis PRO (Oxford Diffraction, 2009); program(s) used to solve structure: SHELXS97 (Sheldrick, 2008); program(s) used to refine structure: SHELXL97 (Sheldrick, 2008); molecular graphics: ORTEP-3 (Farrugia, 1997) and PLATON (Spek, 2009); software used to prepare material for publication: SHELXL97 (Sheldrick, 2008) and PLATON (Spek, 2009).

4.3. General procedure

Synthesis of 10-Phenyl sulfonyl-2-alkyl/aryl-4, 10 Dihydrobenzo [4, 5] imidazo [1,2-a]pyrimidin-4-ones (3a-i)

To a solution of 2- pyrimido [1, 2-*a*] benzimidazol-4(10*H*)-ones (1 mmol) and anhydrous K_2CO_3 (5 mol %) in a solvent mixture of [bmim]Cl and acetonitrile (4:1). Phenyl sulfonyl chloride (1 mmol) was added followed by stirring at room temperature for 18-23 hour. The stirring was continued until the completion of the reaction (TLC). The crude reaction mixture was filtered. The filtrate was quenched with water and extracted with ethyl acetate, finally evaporated and crystallized to get a pure product.

4.4 Physical and Spectral Data of few compounds

4.4.1 **10-(3, 4-dichlorophenyl sulfonyl)-2-(methyl) pyrimido[1,2-a]benzimidazol-4(10H)-one (3a):** Colourless crystal, mp= 205-207 ^oC; ^{1}HNMR ($CDCl_3$, 300MHz): δ = 2.41 (s, 3H), 6.15 (s, 1H), 7.45 (m, 1H), 7.53 (m, 1H), 7.62 (d, 1H), 8.03 (d, 1H), 8.23 (d, 1H), 8.46 (s, 1H), 8.64 (d, 1H). IR (KBr) (vmax /cm^{-1}): 1696, 1613, 1543, 1457, 1278, 1187.

4.4.2 **10-(2, 5-dichlorophenyl sulfonyl)-2-(methyl) pyrimido[1,2-a]benzimidazol-4(10H)-one (3b):** Colourless crystal, mp= 206-208 ^oC; ^{1}HNMR ($CDCl_3$, 300MHz): δ = 2.40 (s, 3H), 6.15 (s, 1H), 7.44 (m, 1H), 7.54 (m, 1H), 7.64 (d, 1H), 8.04 (d, 1H), 8.24 (d, 1H), 8.44 (s, 1H), 8.64 (d, 1H). IR (KBr) (vmax /cm^{-1}): 1690, 1615, 1548, 1457, 1373, 1278, 1135.

4.4.3 **10-(2, 5-dimethoxyphenyl sulfonyl)-2-(methyl) pyrimido[1,2-a]benzimidazol-4(10H)-one (3c):** Colourless crystal; yield: 83%, mp 127-130^oC. IR (KBr) (vmax /cm^{-1}): 3404, 1695, 1541, 1186. ^{1}HNMR ($CDCl_3$, 300MHz): δ = 2.24(s, 3H), 3.41 (s, 3H), 388 (s, 3H), 6.08 (s, 1H) ,6.8 (d, J = 6Hz, 1H),7.1 (m, 1H),7.39-7.44 (m, 1H) 7.49-7.53 (m, 1H), 7.81 (s, 1H), 8.22

(d, J = 6Hz, 1H), 8.6 (d, J = 6Hz, 1H). ^{13}CNMR (CDCI3 100MHz): δ = 24.3, 56.2, 105.5, 113.4, 116.4, 123.5, 125.0, 126.7, 129.5, 146.1, 151.8, 152.6, 159.4, 164.0. MS(EI) m/z 421.2 (M+Na).

4.4.4 **10-(3, 4-dichlorophenyl sulfonyl)-2-(propan-2-yl)pyrimido[1,2-a]benzimidazol-4(10H)-one (3d):** Colourless crystal, yield: 90%, mp 160-162°C. IR (KBr) (vmax /cm^{-1}): 3425, 2972, 1701, 1602, 1188. ^{1}HNMR ($CDCl_3$, 300MHz): δ = 1.29 (d, J = 5.1Hz, 6H), 2.88 (q, J = 5.1Hz, 1H), 6.15 (s, 1H), 7.44 (t, 1H), 7.53 (t, 1H), 7.63 (d, J = 6.6Hz, 1H), 8.03 (d, J = 5.1Hz, 1H), 8.23 (d, J = 6Hz, 1H), 8.42 (s, 1H), 8.62 (d, J = 6Hz, 1H). 13CNMR (CDCl3 100MHz): δ = 21.1, 35.6, 103.9, 114.2, 116.7, 125.2, 127.0, 129.0, 130.8, 132.8, 133.7, 135.8, 136.7, 145.9, 159.2, 172.2. MS (EI) m/z 437 (M+2H).

4.4.5 **10-(2, 5-dichlorophenylsulfonyl)-2-(propan-2-yl)pyrimido[1,2-a]benzimidazol-4(10H)-one (3e):** Colourless crystal, yield: 84%, mp 157-160°C. IR (KBr) (vmax /cm^{-1}): 3433, 2970, 1695, 1604, 1180.MS (EI) m/z 436 (M+H) ^{1}HNMR ($CDCl_3$, 300MHz): δ = 1.07 (d, J = 5.1Hz, 6H), 2.70 (q, J = 5.1Hz, 1H), 6.17 (s, 1H), 7.40-7.57 (m, 4H), 8.24 (d, J = 6Hz, 1H), 8.56 (s, 1H), 8.63 (d, J = 4.8Hz, 1H). ^{13}CNMR (CDCl3 100MHz): δ = 21.0, 35.6, 103.7, 114.0, 116.7, 125.2, 125.9, 127.0, 129.0, 131.5, 132.8, 133.2, 134.6, 135.3, 136.4, 145.9, 159.5, 172.2.

4.4.6 **10-(2, 5-dimethoxyphenylsulfonyl)-2-(propan-2-yl)pyrimido[1,2-a]benzimidazol-4(10H)-one (3f):** Colourless crystal, yield: 85%, mp 180-183 °C; IR (KBr) (vmax /cm^{-1}): 3436, 2962, 1689, 1596, 1188. MS (EI) m/z 428.3 (M+H). ^{1}HNMR ($CDCl_3$, 300MHz): δ = 1.07 (d, J = 5.1Hz, 6H), 2.71 (q, J = 5.1Hz, 1H), 3.40 (s, 3H), 3.87 (s, 3H), 6.08 (s, 1H), 6.79 (d, J = 6.6 Hz, 1H), 7.12 (m, 1H), 7.41 (m, 1H), 7.51 (m, 1H), 7.83 (d, J = 2.4Hz,1H) 8.24 (d, J = 6.3Hz,1H), 8.62 (m, 1H). ^{13}CNMR (CDCI3, 100MHz): δ = 21.6, 36.2, 56.5, 77.1, 103.5, 113.9, 114.7, 116.8, 117.0, 123.7, 124.9, 125.8, 126.2, 127.1, 153.1, 160.4, 172.9.

4.5 Crystallographic analysis of the compounds **3f**

The compound **3f** was crystallized using ethanol by slow evaporation method. The compound **3f** crystallizes in P-1 space group. The molecules are packed in the crystal by the formation by the S–O...N interaction. The molecules are packed in three-dimensions by the S–O...N, S–O...O and C–O...H bonding interaction between them (**Fig. 3**). The Crystal data and other parameters are given in the **Table 3**.

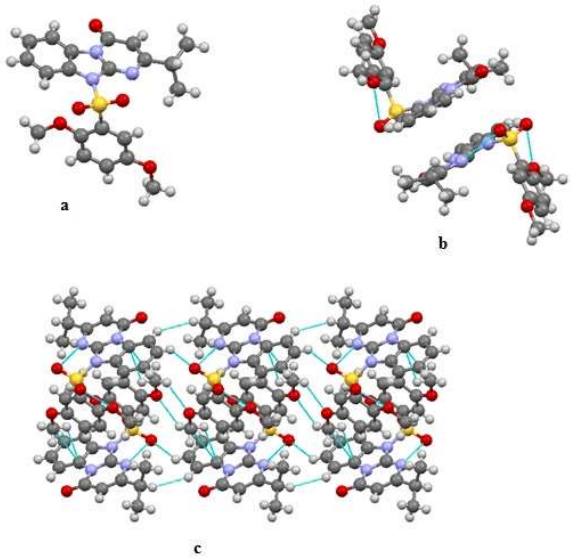

Fig. 3. (a) Shows P-1 space group; (b) shows cyclic N-H...N interaction; (c) shows C-H...O hydrogen bonding interaction

Table 3. Crystal Data and structure Refinement table of the compound **3f**

Compound	**3f**
Identification Code	**CCDC 963951**
Empirical formula	C21 H21 N3 O5 S
Formula weight	427.47
Temperature	293K
Wavelength	0.71073
Crystal System, Space group	Triclinic p-1
Unit Cell Dimensions	a=9.360(3)Å; α=104.714 (17) b=10.277(2) Å; β= 112.47(2) c=11.7791(19)Å; γ= 94.89(2)
Volume	991.4 (5) Å
Z , Density	2, 1.432 g/cm^3
Absorption coefficient	0.203 mm^{-1}
F(000)	448
Crystal Size	0.42mm 0.38mm 0.36mm
Theta min	2.83
Theta max	26.370
h k l max	11,12,14
N ref	4054
R indices(all data)	R:0.0556 (2749); wR2:0.1740(4045)
Npar	275

4.6. Evaluation of TGA analysis of compound 3f

Typical TGA curve (Figure 4) indicate that the thermal behaviour of compound 3f. The corresponding TG process occurred at 290ºC-500 ºC with a mass loss of 67% and showed high thermal stability up to 290ºC

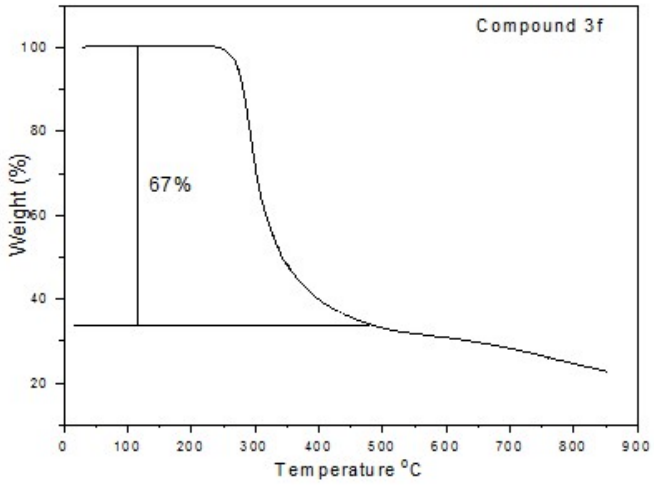

Fig. 4. TGA curves of compound **3f** at a heating rate of 10.0°C/min

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