



J. Serb. Chem. Soc. 76 (8) 1069–1079 (2011)
JSCS–4185

Facile syntheses of Mannich bases of 3-[*p*-(5-arylpyrazolin-3-yl)phenyl]sydnones, as anti-tubercular and anti-microbial agents, under ionic liquid/tetrabutylammonium bromide catalytic conditions

TASNEEM TAJ¹, RAVINDRA R. KAMBLE^{1*}, TEGGINMATH M. GIREESH¹
and RAVINDRA K. HUNNUR²

¹*PG Department of Studies in Chemistry, Karnatak University Dharwad-580 003 and*

²*APL Research Centre, A Division of Aurobindo Pharma Ltd. 313,
Batchupally, Hyderabad-500 072, India*

(Received 8 July 2010, revised 7 January 2011)

Abstract: Novel methylene bridged Mannich bases **2a–j** were synthesized in good to excellent yields from the pyrazoline derivative **1** using various primary/secondary amines, 37 % formalin in presence of ionic liquids/TBAB as catalyst. The structures of the newly synthesized compounds were confirmed by IR, ¹H- and ¹³C-NMR and GC–MS spectroscopy, as well as elemental analysis. The title compounds were screened for their anti-tubercular and antimicrobial activities. Some of the compounds exhibited very good anti-tubercular, antifungal and antibacterial activities.

Keywords: pyrazoline; Mannich base; ionic liquids; TBAB; MIC; anti-tubercular activity.

INTRODUCTION

Multidrug-resistant tuberculosis is perceived as a growing hazard to human health worldwide. The fear is that the number of cases resistant to anti-tubercular drugs is on the increase.¹ One of the strategies suggested for overcoming this problem is to exploit the potential of standard short course chemotherapy based on the cheap and safe first line drugs. Furthermore, there is an urgent need for the development of new potent anti-tubercular drugs without cross resistance with known antimycobacterial agents.^{2,3} This has stimulated scientists to develop novel molecules to combat these illnesses. Pantothenate synthetase (PS) is one of the potential new antimicrobial targets which are useful for the treatment of non-replicating persistent forms of *Mycobacterium tuberculosis* (*Mtb*). Therefore, the

*Corresponding author. E-mail: kamchem9@gmail.com
doi: 10.2298/JSC100708085T

discovery and development of drugs effective against non-replicating persistence (NRP) *Mtb* are considered as the highest priority among tetrabutyl (TB) drug discovery efforts.⁴

Reports convey that Mannich bases possess anti-inflammatory, antibacterial, antifungal and antihistamine activities. The synthesis of pyrazole and its *N*-aryl analogues has been the subject of consistent interest because of the wide range of applications of such heterocycles in the pharmaceutical and agrochemical Industries. Numerous compounds containing the pyrazole moiety have exhibited anti-hyperglycemic, analgesic, anti-inflammatory, antipyretic, antibacterial and sedative-hypnotic activity.⁵⁻⁹ The role of the added pyrazole ring could be to increase the electron density of the system and makes the chromophore more resistant towards enzymatic reduction by radical species. In addition, some sydnone derivatives have been reported as potential anti-tubercular agents.¹⁰

Recently, ionic liquids (ILs), a kind of ion solvent, which combine the advantages of both traditional molecular solvents and melt salts, have been considered as promising new reaction media, and have found wide use in catalytic and non-catalytic reactions as these materials dissolve many organic as well as inorganic substances. In addition, they can be easily recycled. Moreover, their properties are tunable to satisfy specific chemical tasks.¹¹⁻¹⁴

The above observations prompted us to explore the synthetic utility of pyrazoline derivatives using ionic liquids or tetrabutylammonium bromide (TBAB) as catalysts in the synthesis of novel Mannich bases intact with the sydnone moiety, giving novel biodynamic molecules **2a-j** in order to evaluate their antimicrobial and anti-tuberculosis activity.

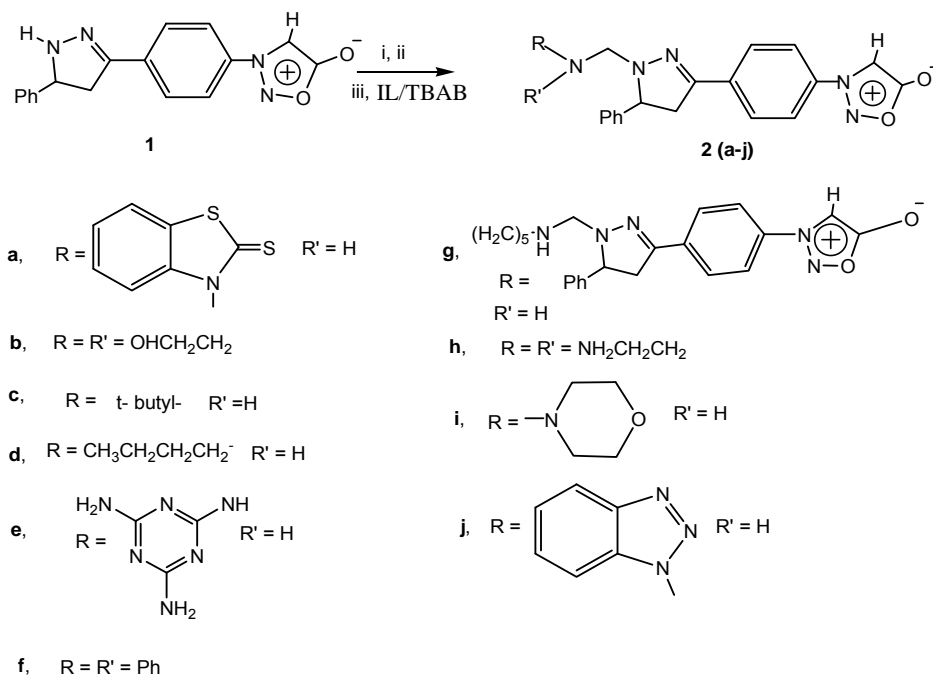
EXPERIMENTAL

Chemistry

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Nicolet Impact 5200 USA FT-IR instrument using KBr pellets. The ¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker Varian 300-MHz FT-NMR spectrometer with TMS as the internal standard. The mass spectra were recorded on Shimadzu Japan QP2010 S spectrometer and the elemental analyses were realized using Heraeus CHN rapid analyzer. The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plates using benzene and ethyl acetate as eluents. The pharmacological evaluations were performed at the Department of Microbiology and Immunology, NGH College of Dental sciences, Belgaum, Karnataka, India. The log *P* values were calculated using ACD/ChemSketch software for the structural analogues of the synthesized compounds and are uncorrected.

The pyrazoline derivative **1** required for the present work was prepared by the reaction of the chalcone and hydrazine hydrate according to a reported method.¹⁵ The acidic ionic liquid catalysts were synthesized according to literature procedures.¹⁶ Commercially available TBAB was used for the reaction at 10 mol %. The pyrazoline derivative **1** upon reaction with primary/secondary amines in presence of 37 % formalin and an ionic liquid as catalyst gave

the Mannich bases **2a–j** (Scheme 1). All the products are solids, with exception of the compounds **2d** and **2f** which were isolated as semisolids.



Scheme 1. Synthesis of Mannich bases **2a–j**.

Preparation of 3-[4-(5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenyl]sydnone (**1**)

The pyrazoline derivative **1** was synthesized according to a literature method.¹⁷ Yellow solid. Yield: 80 %, m.p. 171–173 °C.

Preparation of **2a–j**

To the slurry of compound **1** (0.01 mol), 50 % aqueous ethanol (5 ml) and 37 % formalin (5 ml) was added dropwise an amine (0.01 mol) and an ionic liquid catalyst (0.01 mmol) with cooling and shaking. The reaction mixture was allowed to stand at RT for 1 h with occasional stirring after which it was warmed on a steam bath for 3 h for the conventional synthesis method. When using an ionic liquid 10 mol %, the reaction time was unchanged. The catalyst was recovered by extracting with diethyl ether.

When TBAB was used as catalyst, the reaction time was 2 h. At the end of this period, the solvent was evaporated and the contents were cooled. The products thus separated were filtered and recrystallized (except **2d** and **2f**) in ethanol, petroleum ether and chloroform.

Biological assays

Antimicrobial assay. Preliminary screening was conducted for all the compounds at 100 $\mu\text{g ml}^{-1}$ concentration against two Gram-positive bacteria, *Staphylococcus aureus* – ATCC 25293 and *Bacillus subtilis* – ATCC 6633 and Gram-negative bacteria *Pseudomonas aeruginosa* – ATCC 10145 and *Escherichia coli* – ATCC 35218, and against two fungal strains *Candida albicans* 10231 and *Candida fumigatus* 74359.

The protocol for the antimicrobial activity assay was as follows.¹⁸

Dimethylformamide was used as the solvent control. The bacterial cultures were inoculated on Mueller Hinton Agar (Merck) and fungal cultures on Potato Dextrose Agar. Media (20 ml) were poured into each sterilized Petri dish (99 mm) and media were inoculated homogeneously with the liquid cultures by the spread plate method. All the compounds were dissolved in dimethyl sulfoxide (DMSO) to obtain a concentration of 100 µg/µl. Each sample (100 µl) was directly loaded into the wells of agar plates. The plates inoculated with bacteria were incubated at 37 °C for 24 h and the fungal cultures were incubated at 25 °C for 72 h. All the determinations were performed in triplicate. The standards ampicillin (100 µg ml⁻¹) for the antibacterial and clotrimazole (100 µg ml⁻¹) for the antifungal assays were used as the positive controls and 100 µl of DMSO was used as the negative control. The zones of inhibition were recorded in mm.

Different series of dilutions of the compounds were made (0.5–10.0 µg ml⁻¹) to determine the minimum inhibitory concentration (MIC).

Anti-tubercular assay. The anti-tubercular activity of the test compounds were evaluated against the standard strain of *Mycobacterium tuberculosis* H37Rv. The antibiotic standards used were streptomycin and pyrazinamide. The procedure followed for the anti-tubercular activity assay involved the use of Middlebrook 7H-9 broth. The basal medium was prepared according to the manufacturer's instructions (Hi-Media) and sterilized by autoclaving. Then, 4.5 ml of broth was poured into every sterile bottle. To this, 0.5 ml of albumin dextrose catalase (ADC) supplement consisting of catalase, dextrose and bovine serum albumin (BSA) fraction v was added. Then, a stock solution of the test compound was prepared (10 mg ml⁻¹). From this, appropriate amounts of the solution were transferred to the media bottles to achieve final concentrations of 25, 50, 100 µg ml⁻¹. Finally, 10 µl of a suspension of *M. tuberculosis* H37Rv strain (10⁵ organisms ml⁻¹, adjusted by the McFarland turbidity standard) was transferred to each of the bottles and incubated at 37 °C. Together with these, a growth control without the compound and drug controls were also set up. The bottles were inspected for growth twice a week for a period of three weeks. The appearance of turbidity indicated the growth and inferred resistance to the compound. The growth was confirmed by making a smear from each bottle and performing a Ziehl–Neelsen (ZN) stain.

RESULTS AND DISCUSSION

The synthesis of the investigated compounds by the conventional method resulted into low yields. Use of ionic liquids **1–4** enhanced the yields, but phase transfer catalyst (PTC) method using TBAB gave excellent yields along with increased reaction rates. Various ionic liquids (IL1–IL4) and TBAB catalysts were tried at different concentrations and finally it was observed that 10 mol % of the catalyst (ionic liquids and TBAB) gave good yields (Table I). For the synthesis of long chain alkylated Mannich bases, *viz.*, **2d** and **2g**, IL3 and IL4 gave poor yields as the products could not be isolated in the desired quantity as either solids or semisolids, which posed great difficulty for product characterization. For the other compounds, the catalyst used and the range of yields are depicted in Table II. The ionic liquids which gave better results are also reported. It is interesting to note that the TBAB catalyst gave excellent yields for all the final compounds. The reaction time was unchanged when an ionic liquid (10 mol %)

was used, whereas the use of TBAB reduced the reaction time to 2 h. The ionic liquid Hmim Tsa⁻ (IL1) gave better yields for the final compounds **2a**, **2e** and **2i**, whereas the yields of compounds **2b**, **2c**, **2f** and **2j** were good when Hmim SO₄⁻ (IL2) was used. The catalytic activities of Bmim [H₂PO₄]⁻ (IL3) and Bmim [HSO₄]⁻ (IL4) were much lower and the yields of **2d** and **2h** were negligible under IL3 and IL4 conditions. The ionic liquids IL1 and IL2 did not give the products **2d** and **2g**.

TABLE I. Methods and catalysts employed for the reactions (10 mol %) and the obtained yields

Catalyst	Yield range, %
Conventional method	
Without catalyst	60–70
Ionic liquids method	
Hmim Tsa ⁻ (IL1)	65–75
Hmim SO ₄ ⁻ (IL2)	68–76
Bmim [H ₂ PO ₄] ⁻ (IL3)	30–35
Bmim [HSO ₄] ⁻ (IL4)	25–34
TBAB	80–85

TABLE II. Yields of the respective compounds using the conventional method and employing catalysts

Compound	Method			
	Conventional	Ionic liquids		TBAB
	Yield, %	Catalyst	Yield, %	Yield, %
2a	67	IL1	70	82
2b	65	IL2	72	85
2c	68	IL2	75	84
2d	69	IL3	–	78
2e	70	IL1	70	87
2f	64	IL2	72	89
2g	66	IL4	34	85
2h	67	IL2	74	80
2i	69	IL1	75	88
2j	66	IL2	77	85

The structures of the Mannich bases **2a–j**, given in the Supplementary material, were confirmed by IR, NMR (¹H- and ¹³C-), MS and elemental analyses, the data are also given as Supplementary material. In their IR spectra, all the compounds exhibited a common strong absorption band at around 1748–1754 cm⁻¹ and a medium intensity sharp band at around 2950–3150 cm⁻¹, due to ν(C–H) of sydnone ring. In addition, another common sharp band was observed at around 1580–1595 cm⁻¹, due to C=N stretching frequencies of the pyrazoline ring.

Compound **2a** showed a weak absorption band at around 1420 cm⁻¹ due to C=S stretching. Compound **2b** exhibited a broad band at about 3427 cm⁻¹ due to

the two OH groups. Similarly, **2c** and **2d** showed sharp medium bands at 3426 and 3444 cm^{-1} arising from N–H stretching. Two weak stretching bands at around 3405 and 3415 cm^{-1} were present in the spectrum of compound **2e** due to the symmetric and asymmetric stretching frequencies of NH_2 groups attached to the triazine ring. Compound **2g** did not show any other significant bands except strong absorption at 2930 and 2922 cm^{-1} due to CH_2 stretching. Compound **2h** also presented two weak bands at around 3439 and 3445 cm^{-1} due to N–H stretching. Compounds **2i** and **2j** did not show any other significant stretching bands.

The ^1H -NMR spectral analysis of the title compounds resulted in the following observations. All the compounds gave a singlet in the range δ 6.65–6.75 ppm due to the proton attached at the C_4 carbon of the sydnone ring. The protons of the pyrazole ring, *i.e.*, the methine proton and the diastereotopic methylene protons exhibited a characteristic ABX pattern. The methylene protons can be assigned as H_A and H_B and the methine proton as H_x . H_A and H_B are diastereotopic and also anisochronous as they differ in their chemical shift and since this difference is not large, they are identified as AB protons. The methine proton on the adjacent carbon with a larger downfield shift is the H_x proton and all together, they form an ABX pattern. The H_A and H_B protons appear as doublet of doublets due to geminal and vicinal coupling. These H_A and H_B differ in coupling with H_x and hence they are also anisogamous. The H_A proton appears as a doublets of doublet in the range δ 3.48–3.73 ppm with two coupling constants, $J_{\text{AB}} = 17.6$ Hz and $J_{\text{Ax}} = 4.5$ Hz. H_B also appears as doublet of doublets at 3.08–3.47 ppm, whereby $J_{\text{BA}} = 17.6$ Hz and $J_{\text{Bx}} = 11.8$ Hz. The H_x proton always appears as a four-line spectrum with $J_{\text{xA}} = 4.49$ Hz and $J_{\text{xB}} = 11.84$ in the δ range 4.32–4.92 ppm. The methylene protons attached to the nitrogen of pyrazole appear in the δ range 3.50–3.75 ppm.

The ^1H -NMR spectrum of **2a** showed a singlet at δ 3.45 ppm for two protons due to presence of methylene groups. The aromatic protons appear as a multiplet in the δ range 7.32–7.76 ppm due to protons on benzothiazoline-2-thione and the phenyl ring attached to the pyrazoline ring. The ^1H -NMR spectrum of **2b** showed a singlet at δ 3.64 ppm for two protons due to the presence of methylene groups attached to the nitrogen atom of the pyrazoline ring. The remaining two sets of methylene groups appeared as two sets of triplets at δ 4.38 (those attached to nitrogen) and 4.83 ppm (those attached to the OH group). The aromatic protons appeared as a multiplet in the region δ 7.27–7.87 ppm for nine protons.

Compound **2c** exhibited the following ^1H -NMR signature. A singlet for 9 protons was observed at δ 1.78 ppm due to *t*-butyl and another singlet at δ 3.64 ppm for 2 protons due to the methylene group. Similarly, a broad singlet was observed at 5.15 ppm (D_2O exchangeable) due to NH protons. Compound **2d** showed a singlet at δ 3.71 ppm due to the methylene group present in between the pyrazoline ring and the butylamine moiety and another singlet at δ 4.92 ppm (D_2O

exchangeable). The *n*-butyl group attached to the nitrogen atom gave a triplet at δ 1.05 ppm due to the methyl protons and another triplet in the range δ 4.11 ppm due to methylene protons attached to the nitrogen. The two methylene groups present in between the methyl and the methylene adjacent to the nitrogen appear as a multiplet in the range δ 2.70–2.96 ppm. The aromatic protons appear as multiplets in the region δ 6.77–7.83 ppm.

Compound **2e** showed a singlet at δ 3.71 ppm and a broad singlet at δ 5.08 (D₂O exchangeable) due to NH₂ protons, whereas compound **2f** showed a complex multiplet within the range 7.03–8.21 ppm for 19 aromatic protons. A multiplet at δ 1.34–2.40 ppm of 10 aliphatic protons was observed for compound **2g**, in which the 5 methylene group chain is flanked by two pyrazoline phenylsydnone groups. This compound also exhibited two doublets of doublets for 4 protons and one four line spectrum as a doublet of doublets for 2 methine protons, one in each lead pyrazoline ring. Compound **2h** showed a multiplet for 4 protons at δ 0.88–2.17 ppm due to the two sets of methylene protons attached to nitrogen atoms and another set of 2 protons as a singlet at 3.53 ppm.

A multiplet at δ 2.45–2.63 ppm appeared due to the methylene protons of morpholine in the spectrum of compound **2i**. Compound **2j** exhibited a singlet due to the methylene group spaced between the benzotriazole and the pyrazole ring at δ 3.75 ppm. The aromatic protons appeared as multiplet in the range δ 7.28–7.89 ppm.

The ¹³C-NMR spectra of all the compounds showed signals in the respective regions.

Furthermore, in the electron impact studies, all the compounds showed molecular ion peaks at their respective *m/z* value.

Antibacterial activity assay

The MIC values for compounds **2a–j** and the standard obtained in the *in vitro* anti-bacterial studies, which ranged from 0.5–4 $\mu\text{g ml}^{-1}$, are given in Table III. These activities are comparable to those of a number of common pyrazole derivatives reported in the literature. The anti-bacterial activity of all the compounds against *S. aureus*, *B. subtilis*, *P. aeruginosa* and *E. coli* showed good potencies compared to the control drug ampicillin. From the results, it is apparent that among the synthesized compounds **2a**, **2b** and **2f** showed excellent activity against *B. subtilis* with MIC values 0.5–1.5 $\mu\text{g ml}^{-1}$, and *P. aeruginosa* with values of 1–2.5 $\mu\text{g ml}^{-1}$. Compounds **2c**, **2e**, **2f**, **2h** and **2j** showed potent inhibition against *S. aureus* with values ranging from 1–3 $\mu\text{g ml}^{-1}$. Compounds **2a**, **2f** and **2j** showed good activity against *E. coli* with values of 1–3 $\mu\text{g ml}^{-1}$. Among the ten screened compounds, almost all of them exhibited promising inhibition against the bacterial cultures compared to the control drug ampicillin.

Antifungal activity assay

The *MIC* values for compounds **2a–j** and the standard in the *in vitro* anti-fungal studies are represented in Table III. Among the test compounds, interesting activities were found for compounds **2a**, **2b**, **2f**, **2e**, **2g**, and **2i**, which showed potent inhibition against *C. albicans* with *MIC* values in the range 1.5–3 $\mu\text{g ml}^{-1}$. Compounds **2b**, **2c** and **2i** possessed favorable *MIC* values against *C. fumigatus*, having values in the range 2–3.5 $\mu\text{g ml}^{-1}$. The anti-fungal activities indicated that some of the derivatives exhibited a broad spectrum of activity against the tested fungi, with compounds having electron donating groups appended to the pyrazole moiety exhibiting a better spectrum of activity than the reference drug clotrimazole.

TABLE III. Antibacterial and antifungal activities (*MIC* / $\mu\text{g ml}^{-1}$) of the compounds **2a–j** (control: DMSO)

Entry No.	<i>B. subtilis</i> ATCC 6633	<i>S. aureus</i> ATCC 25293	<i>E. coli</i> ATCC 35218	<i>P. aeruginosa</i> ATCC 10145	<i>C. albicans</i> ATCC 10145	<i>C. fumigatus</i> ATCC 74359
2a	1.5	1	3	3.5	3	2
2b	2	1	2	3.5	4	3.5
2c	0.5	3	1.5	2	1.5	3.5
2d	0.5	3	1	2.5	2	2.5
2e	0.5	2.5	2	2	3	2
2f	1	3	3	3.5	3.5	2
2g	0.5	1.5	2	1	4	3
2h	0.5	2	2	2	2	3
2i	1	2	2	1.5	3	2
2j	1	2	3	1.5	1.5	2.5
Ampicillin	0.5	1	2	2	–	–
Clotrimazole	–	–	–	–	2	2

Anti-tubercular activity assay

The results of the anti-tubercular activity studies are given in Table IV, from which it can be seen that the compounds with electron donating groups *viz.*, **2c**, **2d**, **2e**, **2g** and **2i** exhibited excellent inhibition (*MIC*) at a concentration of less than 5 $\mu\text{g ml}^{-1}$. Compounds **2b**, **2f**, **2h** and **2j** showed moderate inhibition at a concentration of 10 $\mu\text{g ml}^{-1}$. Compound **2a** with benzothiazoline-2-thione showed activity only at a concentrations of 25 $\mu\text{g ml}^{-1}$ as compared to the standards used, *viz.*, streptomycin (7.5 $\mu\text{g ml}^{-1}$) and pyrazinamide (10 $\mu\text{g ml}^{-1}$). The encouraging activities are attributed to the presence of long alkylating chains with electron donating groups, *viz.*, OH, NH₂, methylene and ethylene through mesomeric effect, appended to the pyrazoline moiety.

The log *P* values of the compounds are given in Table V. To qualify a compound as a drug candidate, it is analyzed by the parameters set by the Lipinski rule of five. The log *P* value is an important physico-chemical property indi-

cating lipophilicity and the ability of a molecule to cross the various biological membranes. According to the Lipinski rule of five, with a log *P* value below 5, it is feasible for a compound to be future drug. The synthesized compounds showed marginal lipophilicity within the range of 1.20–5.0. The molecular weight of a compound is related to its *in vivo* administration. All the synthesized compounds had a molecular weight within the acceptable range, *i.e.*, 400–500 g mol⁻¹.

TABLE IV. Anti-tubercular activity of the synthesized compounds (Strain H37Rv); standard: streptomycin, 7.5 µg ml⁻¹, pyrazinamide, 10 µg ml⁻¹; all compounds tested at concentrations of 5, 10 and 25 µg ml⁻¹

Entry No.	MIC / µg ml ⁻¹
2a	25
2b	4.5
2c	5
2d	3.5
2e	5
2f	10
2g	5
2h	10
2i	3.5
2j	12

TABLE V. The calculated log *P* values of the newly synthesized compounds

Entry No.	log <i>P</i>
1	1.83
2a	3.73
2b	1.49
2c	2.41
2d	2.77
2e	1.20
2f	5.03
2g	Not applicable
2h	1.38
2i	1.62
2j	2.96
INH	0.887
Nifuroxazide	0.059

According to the Lipinski rule, a less than five-heteroatom moiety can be considered as a probable candidate as a drug. The log *P* values depict the penetration of the drug into the cell membrane. As value of log *P* value increases, the penetration also increases. Compounds **2b**, **2c**, **2d**, **2e** and **2i** showed low *MIC* values and high log *P* values, which show that these moieties have better penetration values and can be considered for further studies as drugs.

CONCLUSIONS

A simple and efficient method for the synthesis of novel methylene-bridged Mannich bases of benzothiazoline-2-thione, morpholine, biphenyl and benzotriazole derivatives was developed. It is believed that the procedural simplicity, the efficiency and the easy accessibility of the reaction partners give access to a wide array of heterocyclic frameworks equipped with a pendant pyrazoline unit. The use of environmental friendly catalysts, *viz.*, an ionic liquid and TBAB is an added advantage. TBAB as a catalyst gave excellent results in terms of yields.

The results of the anti-tubercular screening revealed that of the ten synthesized compounds, five showed good inhibition while the other five compounds displayed moderate to low inhibition.

SUPPLEMENTARY MATERIAL

Structures of the prepared compounds and their spectral data are available electronically at <http://www.shd.org.rs/JSCS/>, or from the corresponding author on request.

ИЗВОД

ЈЕДНОСТАВНА СИНТЕЗА МАНИХОВИХ БАЗА 3-[*p*-(5-АРИЛ-ПИРАЗОЛИН-3-ИЛ)-ФЕНИЛ]СИДНОНА У ПРИСУСТВУ КАТАЛИТИЧКИХ КОЛИЧИНА ТВАВ/ЈОНСКЕ ТЕЧНОСТИ, КАО АНТИ-ТУБЕРКУЛОЗНИХ И АНТИ-МИКРОБНИХ АГЕНАСА

TASNEEM TAJ¹, RAVINDRA R. KAMBLE¹, T. M. GIREESH¹ и RAVINDRA K. HUNNUR²

¹PG Department of Studies in Chemistry, Karnatak University Dharwad-580 003 и ²APL Research Centre, A Division of Aurobindo Pharma Ltd. 313, Batchupally, Hyderabad-500 072, India

Синтетисане су нове Манихове базе **2a-j**, у добром до одличном приносу, полазећи од пиразолинског деривата **1** употребом различитих примарних/секундарних амина и 37 % формалдехида, у присуству каталитичких количина ТВАВ/јонске течности. Структура нових једињења потврђена је IC, NMR (¹H-, ¹³C-), GC-MS и елементалном анализом. Испитана је антитуберкуозна и антимикробна активност добијених једињења. Нека од њих показују веома добру антитуберкуозну, антифунгалну и антибактеријску активност.

(Примљено 8. јула 2010, ревидирано 7. јануара 2011)

REFERENCES

1. S. Rollas, S. Güniz Küçükgülzel, *Molecules* **12** (2007) 1910
2. T. AbouI-Fadl, A. H. Faragany Mohammed, E. A. S. Hassan, *Arch. Pharm. Res.* **26** (2003) 778
3. R. K. Mali, R. R. Somani, M. P. Toraskar, K. K. Mali, P. P. Naik, P. Y. Shirodkar, *Int. J. Chem. Tech. Res.* **1** (2009) 168
4. S. Velaparthy, M. Brunsteiner, R. Uddin, B. Wan, S. G. Franzblau, P. A. Petukhov, *J. Med. Chem.* **51** (2008) 1999
5. S. Peruncheralathan, T. A. Khan, H. Ila, H. Junjappa, *J. Org. Chem.* **70** (2005) 10030
6. K. L. Kees, J. J. Fitzgerald, K. E. Steiner Jr., J. F. Mattes, B. Mihan, T. Tosi, D. Mondoro, M. L. McCaleb, *J. Med. Chem.* **39** (1996) 3920
7. S. Manfredini, R. Bazzanini, P. G. Baraldi, M. Guarneri, D. Simoni, M. E. Marongiu, A. Pani, E. Tramontano, P. L. Colla, *J. Med. Chem.* **6** (1992) 917

8. L. N. Jungheim, *Tetrahedron Lett.* **30** (1989) 1889
9. P. Kim, S. Kang, H. I. Boshoff, J. Jiricek, M. Collins, R. Singh, U. H. Manjunatha, P. Niyomrattanakit, L. Zhang, M. Goodwin, T. Dick, T. H. Keller, C. S. Dowd, C. E. Barry, *J. Med. Chem.* **52** (2009) 1329
10. J. J. Jogul, B. V. Badami, *J. Serb. Chem. Soc.* **71** (2006) 851
11. A. C. Cole, J. L. Jensen, I. Ntai, K. L. T. Tran, K. J. Weaver, D. C. Forbes, J. H. Davis Jr., *J. Am. Chem. Soc.* **124** (2002) 5962
12. T. Welton, *Chem. Rev.* **99** (1999) 2071
13. P. Wasserscheid, W. Keim, *Angew. Chem. Int. Ed.* **39** (2000) 3773
14. R. Sheldon, *Chem. Commun.* **23** (2001) 2399
15. G. Zhao, T. Jiang, H. Gao, B. Han, J. Huang, D. Sun, *Green Chem.* **6** (2004) 75
16. G. V. P. Rao, P. N. Reddy, Y. T. Reddy, V. N. Kumar, B. Rajitha, *Ind. J. Chem.* **44B** (2005) 1109
17. D. B. Dambal, P. P. Pattanashetti, R. K. Tikare, B. V. Badami, G. S. Puranik, *Indian J. Chem.* **23B** (1984) 186
18. A. M. Revol-Junelles, R. Mathis, F. Krier, A. Delfour, G. Lefebvre, *Lett. Appl. Microbiol.* **23** (1996) 120.

Copyright of Journal of the Serbian Chemical Society is the property of National Library of Serbia and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.