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Synthesis of ethoxyphthalimido derivatized thiazolodihydropyridines assembled with pyrazole and isoxazole systems from common intermediate chalcone and evaluation of their antibacterial activity

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Condensation of aromatic aldehydes, malononitrile and thioglycolic acid gives 5-amino-3-oxo-7-substitutedphenyl-2-substitutedarylidene-2,3-dihydro-7*H*-[1,3]thiazolo[3,2-*a*] pyridine-6,8-dicarbonitrile **1a-e**. This acts as key intermediate for two series of final compounds **4a-e** and **7a-e**. In the first route compounds **1a-e** are refluxed with hydroxylamine hydrochloride to yield tricyclic compound 8-amino-3,6-bis(substitutedphenyl)-1,3,3*a*,9*a*-tetrahydro-6*H*-isoxazolo[3',4':4,5]-[1,3]thiazolo[3,2-*a*]pyridin-5,7-dicarbonitrile **2a-e**. These when condensed with isatin give the corresponding Schiff bases **3a-e**. Condensation of **3a-e** with bromoethoxyphthalimide give the final products 8-[(1*N*-ethoxyphthalimido-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)amino]-3,6-bis(substitutedphenyl)-1,3,3*a*,9*a*-tetrahydro-6*H*-isoxazolo[3',4':4,5] [1,3]thiazolo-[3,2-*a*]pyridine-5,7-dicarbonitrile **4a-e**. In the second pathway NH_2 group of compounds **1a-e** is protected by bezoylation to furnish **5a-e**. These α,β-unsaturated compounds (ring chalcones) when treated with hydrazine hydrate undergo cyclization to form *N*-(5,7-dicyano-3,6-diphenyl-2*H*,6*H*-pyrazolo[3',4':4,5][1,3]thiazolo[3,2-*a*] pyridine-8-yl)benz- amide **6a-e**. Active hydrogen of their pyrazole ring is replaced by ethoxyphthalimido moiety to afford the final compounds *N*-(5,7-dicyano-3,6-bis (substitutedphenyl)-2*N*-ethoxyphthalimido-2*H*,6*H*-pyrazolo[3',4':4,5][1,3]thiazolo[3,2-*a*] pyridine-8-yl)benzamide **7a-e**. The structures of synthesized compounds have been assigned on the basis of elemental analysis and spectral data.

Keywords: Malononitrile, thioglycolic acid, triethylamine, piperidine, isatin

1,4-Dihydropyridines are important Ca^{2+} channel regulators[1] and are mainly used to treat cardiovascular diseases such as hypertension and congestive cardiopathy[2,3]. The role of 1,4-dihydropyridines as chemotherapeutic agents having roles such as counteracting multidrug resistance, reversal in tumor cell proliferation, potential immunodulating and antitubercular activity[4] is well studied. Pyrazole ring is a five membered heterocyclic structure containing two continuous nitrogen atoms. Pyrazole motif makes up the core structure of numerous biologically active compounds, including blockbuster drugs such as Celebrex[5] and Viagra[6], which find a wide range of applications in pharmaceutical and agrochemical industries[7]. Pyrazole derivatives have been used as 5α-reductase inhibitor[8], blood platelet aggregation inhibitor[9], antibacterial[10], antifungal, anticancer[11], anti-inflammatory[12], adenosine antagonist[13], herbicidal, antiparasitic, antipyretic[14] and antidiabetic[15] agents and inhibitor of enoyl-ACP reductase of *Plasmodium falciparum*[16]. Isoxazole derivatives represent an important class of N,O-containing heterocycles possessing diverse useful bioactivities like antiarthritic[17], anti-inflammatory[18], antimicrobial[19], antitumor[20], antitubercular[21], antifungal[22], antiviral[23], anesthetic, anticancer, hypolipidemic[24], antiarrhythmic[25], insect antifeedant[26], acetyl cholinesterase inhibitor[27], glycogen phophorylase inhibitor[28], antipsychotic[29], anticoagulant[30], PPAR agonist[31], *etc*. Several derivatives of alkoxyphthalimide have been synthesized[32] and reported to demonstrate a wide range of pharmacological activities like anticancer, antimalarial[33], antiepileptic[34], *etc*.

In view of above mentioned facts and in continuation with the ongoing work on the synthesis of alkoxyphthalimide derivatives of heterocycles, it appeared expedient to synthesize 8-[(1*N*-ethoxyphthalimido-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)-amino]-3,6-bis(substitutedphenyl)-1,3,3*a*,9*a*-tetrahydro-6*H*-isoxazolo[3',4':4,5][1,3]thiazolo[3,2-*a*]pyridine-5,7-dicarbonitrile and *N*-(5,7-dicyano-3,6-bis(substitutedphenyl)-2*N*-ethoxy-phthalimido-2*H*,6*H*-pyrazolo[3',4':4,5][1,3]thiazolo[3,2-*a*]pyridine-8-yl)benzamide *via* a series of reactions.

Results and Discussion

Three component cyclocondensation of aromatic aldehydes, malononitrile and thioglycolic acid in absolute ethanol and in the presence of catalytic amount of triethylamine/piperidine yielded **1a-e** in good yields. Structures of **1a-e** were determined on the basis of elemental analysis, IR, ^{1}H NMR and mass spectra. The IR spectrum of thiazolopyridine **1a** showed primary amino band at 3410 cm^{-1} and 3370 cm^{-1} and a cyano stretch at 2140 cm^{-1}. ^{1}H NMR spectrum of **1a** in DMSO-d_6 showed a signal in the region δ 4.62 attributed to the pyridine[35] H. Mass spectrum of **1e** is fully consistent with the assigned structure. Compound **1a** revealed its molecular ion peak at *m/z* 382 (17.8%) corresponding to its molecular formula. Other derivatives gave additional peaks at 1050 cm^{-1} due to C-O stretching (OMe, **1b**), 785 cm^{-1} due to C-Cl stretching (**1c**), 1510 cm^{-1} due to N-O stretching (NO_2, **1e**) in IR spectra and δ 3.62 (s, 3H, OCH_3), δ 2.87 (s, 6H, NMe_2) in ^{1}H NMR spectra. In the first route (**Scheme I**) cyclization of **1a-e** with hydroxylamine hydrochloride was carried out in the presence of sodium acetate in hot acetic acid in ethanolic media to give **2a-e**. Formation of **2a-e** was confirmed by chemical tests and spectral studies. A strong band at 1690 cm^{-1} for C=O group in IR region and δ 6.25 due to ArCH=C group in ^{1}H NMR disappeared which were present in compounds **1a-e**. Appearance of N-O stretch at 1480 cm^{-1} in IR region confirms the formation of isoxazol ring. Condensation of isatin with amino group of **2a-e** in absolute methanol in the presence of trace of acetic acid was confirmed by appearance of a band at 1670 cm^{-1} due to keto group in the IR spectra, and in ^{1}H NMR peak at δ 10.20 for cyclic NH group. Condensation of **3a-e** with bromoethoxyphthalimide in the presence of pyridine/NaH gave **4a-e**. Spectral studies confirm its formation. Free stretching vibration band for NH group at 3368-3340 cm^{-1}, which was present in compounds **3a-e** due to NHCO group, had disappeared and a strong band at 1290-1200 cm^{-1} appeared for the C-N stretching of CH_2NCO group, confirm the formation of C-N bond. Reaction conditions, however, depend upon the aromatic substituents.

In the second route **1a-e** were treated with benzoyl chloride in dilute alkaline media to protect the free NH_2 group present in **1a-e**. These compounds **5a-e** were then refluxed with hydrazine hydrate (cautiously) in ethanolic media to furnish **6a-e**. Formation of these were confirmed by disappearance of C=O stretching band at 1710 cm^{-1} in IR region and δ 6.23 for ArCH=C group in ^{1}H NMR spectra. Appearance of NH band at 3370 cm^{-1} in IR spectra and δ 7.9 in ^{1}H NMR spectra confirms the formation of pyrazole ring. These were further condensed with bromoethoxyphthalimide to give the final products **7a-e**.

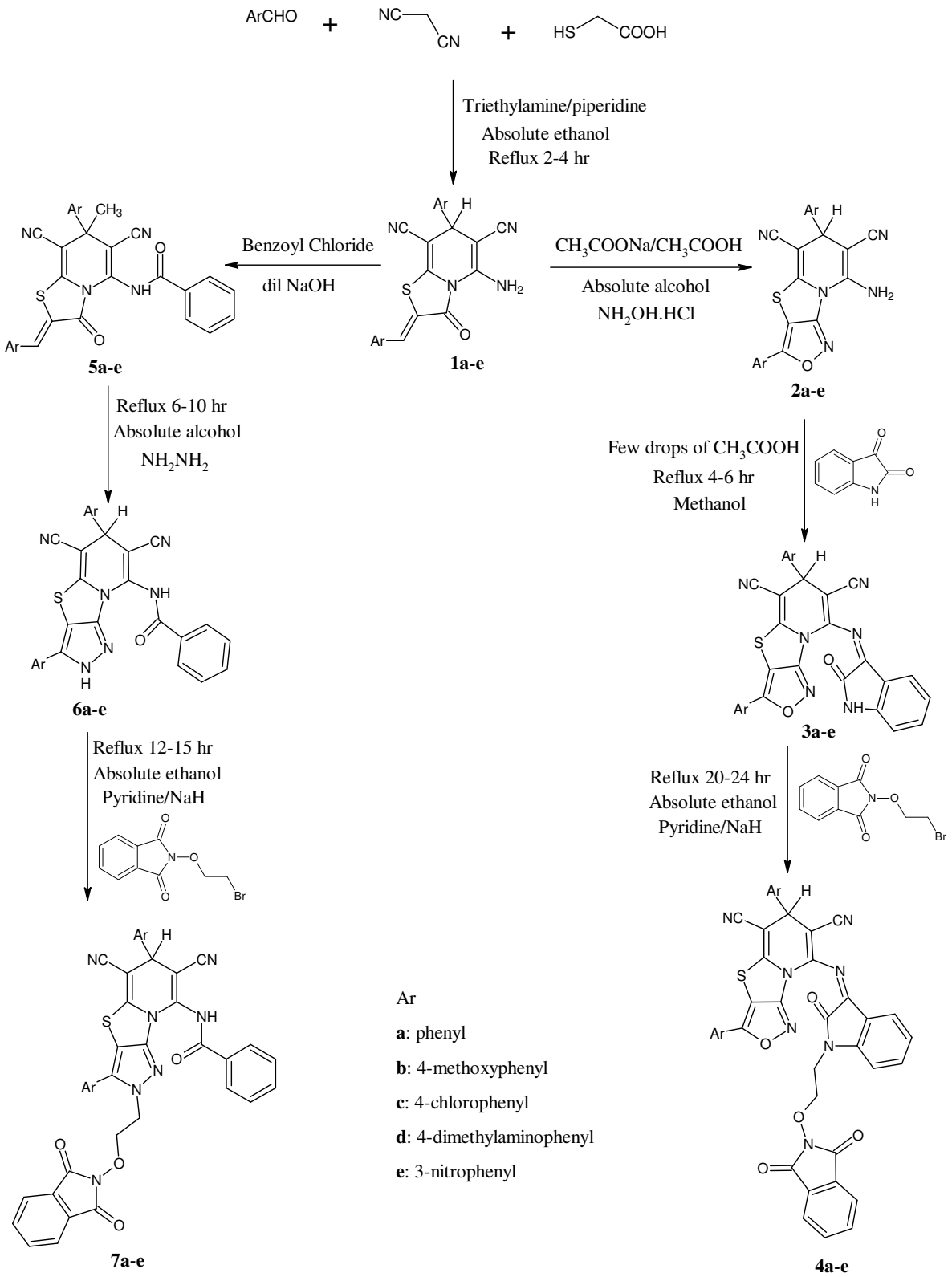
Experimental Section

The reagent grade chemicals were purchased from commercial sources and purified by either distillation or recrystallization before use. Homogeneity of the compounds was checked on silica G TLC plates of 2 mm thickness using *n*-hexane and ethyl acetate as solvent system. The visualization of spots was carried out in an iodine chamber. Melting points of all synthesized compounds were obtained in open capillaries and are uncorrected. The IR spectra of the compounds were recorded in the 4000-450 cm^{-1} range using KBr discs on FTIR IR RXI Perkin-Elmer spectrometer and ^{1}H NMR spectra were recorded on a Bruker DRX-300 MHz spectrometer (300 MHz) in $CDCl_3$/DMSO-d_6 using TMS as internal standard with the chemical shifts expressed in δ (ppm). The FAB mass spectra were recorded on a Jeol SX-102 (FAB) spectrometer using Argon/Xenon (6 kV, 10 mA) as FAB gas.

Synthesis of 5-amino-3-oxo-7-substitutedphenyl-2-substitutedarylidene-2,3-dihydro-7*H*-[1,3]thiazolo[3,2-*a*]pyridine-6,8-dicarbonitrile, 1a. A mixture of benzaldehyde (0.02 mole, 2.00 mL), malononitrile (0.02 mole, 1.32 mL) and thioglycolic acid (0.01 mole, 0.7 mL) in absolute ethanol (20 mL) was refluxed for 2 hr in the presence of triethylamine or piperidine (0.5 mL). The reaction mixture was cooled at RT and poured into crushed ice/dil HCl. The solid obtained was filtered, washed, dried and purified by recrystallization from absolute alcohol. IR (KBr): 3410, 3370 (N-H str.), 3070 (C-H str., Ar-H), 2140 (C≡N str.), 1690 cm^{-1} (C=O str.); ^{1}H NMR ($CDCl_3$): δ 7.85-7.46 (m, 10H, Ar-H), 6.82 (s, 2H, NH_2), 6.25 (s, 1H, C=CHAr), 4.62 (s, 1H, H of pyridine).

Similarly, compounds **1b-e** were prepared with small changes in reflux time and reaction work-up procedures. Their characteristic analytical data are given in **Table I** and spectral data are given below.

1b: IR (KBr): 3415, 3367 (N-H str.), 3120 (C-H str., Ar-H), 2156 (C≡N str.), 1050 (C-O str.), 2964 (C-H str., CH_3), 1695 cm^{-1} (C=O str.); ^{1}H NMR ($CDCl_3$): δ 7.78-7.24 (m, 8H, Ar-H), 6.86 (s, 2H, NH_2), 3.62 (s, 3H, OCH_3), 6.20 (s, 1H, C=CHAr).


ArCHO
Triethylamine/piperidine
Absolute ethanol
Reflux 2-4 hr
Benzoyl Chloride
dil NaOH
CH3COONa/CH3COOH
Absolute alcohol
NH2OH.HCl
1a-e
2a-e
5a-e
Reflux 6-10 hr
Absolute alcohol
NH2NH2
6a-e
Few drops of CH3COOH
Reflux 4-6 hr
Methanol
3a-e
Reflux 12-15 hr
Absolute ethanol
Pyridine/NaH
Reflux 20-24 hr
Absolute ethanol
Pyridine/NaH
7a-e
4a-e
Ar
a: phenyl
b: 4-methoxyphenyl
c: 4-chlorophenyl
d: 4-dimethylaminophenyl
e: 3-nitrophenyl

Scheme I

1c: IR (KBr): 3440, 3375 (N-H str.), 3160 (C-H str., Ar-H), 2100 (C≡N str.), 785 (C-Cl str.), 1660 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 7.82-7.46 (m, 8H, Ar-H), 6.89 (s, 2H, NH_2), 6.28 (s, 1H, C=CHAr).

1d: IR (KBr): 3442, 3398 (N-H str.), 3030 (C-H str., Ar-H), 2170 (C≡N str.), 2920 cm^{-1} (C-H str., CH_3); ^1H NMR ($CDCl_3$): δ 7.77-7.26 (m, 8H, Ar-H), 6.84 (s, 2H, NH_2), 2.87 (s, 6H, $N(CH_3)_2$), 6.30 (s, 1H, C=CHAr).

1e: IR (KBr): 3447, 3365 (N-H str.), 3080 (C-H str., Ar-H), 2134 (C≡N str.), 1510 (N-O str.), 1694 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 7.69-7.28 (m, 8H, Ar-H), 6.83 (s, 2H, NH_2), 6.26 (s, 1H, C=CHAr), 2.84 (s,6H, NMe_2).

Synthesis of 8-amino-3,6-bis(substitutedphenyl)-1,3,3*a*,9*a*-tetrahydro-6*H*-isoxazolo[3',4':4,5][1,3]-thiazolo[3,2-*a*]pyridine-5,7-dicarbonitrile, 2a. Anhydrous sodium acetate (0.02 mole, 1.64 g) was dissolved in a minimum amount of hot acetic acid. Compound **1a** (0.01 mole, 3.82 g) was taken in absolute ethanol (10 mL) and to it hydroxylamine hydrochloride (0.01 mole, 0.69 g) in absolute ethanol (10 mL) was added. The solution of sodium acetate was transferred to this reaction mixture and refluxed for 10 hr. It was then cooled and poured into crushed ice, the product obtained was filtered, washed and purified by recrystallization from ethanol. IR (KBr): 3460, 3340 (N-H str.), 3030 (C-H str., Ar-H), 2134 (C≡N str.), 1480 cm^{-1} (N-O str.); ^1H NMR ($CDCl_3$): δ 7.78-7.30 (m, 10H, Ar-H), 6.81 (s, 2H, NH_2).

Compounds **2b-e** were also prepared by similar method with minor change in reaction conditions. Their characteristic analytical data are mentioned in **Table I** and spectral data are given below.

2b: IR (KBr): 3425, 3330 (N-H str.), 3085 (C-H str., Ar-H), 1064 (C-O str.), 2940 (C-H str., CH_3), 2175 (C≡N str.), 1520 cm^{-1} (N-O str.); ^1H NMR ($CDCl_3$): δ 7.88-7.50 (m, 8H, Ar-H), 6.80 (s, 2H, NH_2), 3.66 (s, 3H, OCH_3).

2c: IR (KBr): 3436, 3380 (N-H str.), 3135 (C-H str., Ar-H), 795 (C-Cl str.), 2156 (C≡N str.), 1560 cm^{-1} (N-O str.); ^1H NMR ($CDCl_3$): δ 7.70-7.37 (m, 8H, Ar-H), 6.85 (s, 2H, NH_2).

2d: IR (KBr): 3445, 3392 (N-H str.), 3152 (C-H str., Ar-H), 2955 (C-H str., CH_3), 2160 (C≡N str.), 1445 cm^{-1} (N-O str.); ^1H NMR ($CDCl_3$): δ 7.43-7.16 (m, 8H, Ar-H), 6.81 (s, 2H, NH_2), 2.87 (s, 6H, $N(CH_3)_2$).

2e: IR (KBr): 3423, 3350 (N-H str.), 3190 (C-H str., Ar-H), 2140 (C≡N str.), 1590 cm^{-1} (N-O str.); ^1H NMR ($CDCl_3$): δ 7.93-7.53 (m, 10H, Ar-H), 6.85 (s, 2H, NH_2).

Synthesis of 8-[(2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)amino]-3,6-diphenyl-1,3,3*a*,9*a*-tetrahydro-6*H*-isoxazolo[3,4:4,5][1,3]thiazolo[3,2-*a*]pyridine-5,7-dicarbo- nitrile, 3a. Compound **2a** (0.01 mole, 3.99 g) was dissolved in methanol. Isatin (0.01 mole, 1.47 g) and few drops of acetic acid were added to the reaction mixture. The reaction mixture was refluxed for 6 hr and excess of solvent was evaporated under reduced pressure. The solid obtained was dried and purified by recrystallization from ethanol. IR (KBr): 3340 (N-H str.), 3082 (C-H str., Ar-H), 1670 (C=O str.), 2158 (C≡N str.), 1536 cm^{-1} (N-O str.); ^1H NMR ($CDCl_3$): δ 7.78-7.40 (m, 14H, Ar-H), 10.20 (s, 1H, NH of indole).

Compounds **3b-e** were also prepared by similar methods with minor change in reaction conditions. Their characteristic analytical data are mentioned in **Table I** and spectral data are given below.

3b: IR (KBr): 3360 (N-H str.), 3058 (C-H str., Ar-H), 1080 (C-O str.), 2934 (C-H str., CH_3), 2154 (C≡N str.), 1564 (N-O str.), 1692 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 7.82-7.39 (m, 12H, Ar-H), 10.28 (s, 1H, NH of indole), 3.64 (s, 3H, OCH_3).

3c: IR (KBr): 3350 (N-H str.), 3145 (C-H str., Ar-H), 790 (C-Cl str.), 2170 (C≡N str.), 1510 (N-O str.), 1650 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 7.64-7.35 (m, 12H, Ar-H), 10.24 (s, 1H, NH of indole).

3d: IR (KBr): 3368 (N-H str.), 3065 (C-H str., Ar-H), 2950 (C-H str., CH_3), 2172 (C≡N str.), 1484 (N-O str.), 1685 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 7.55-7.30 (m, 12H, Ar-H), 10.45 (s, 2H, NH_2), 2.85 (s, 6H, $N(CH_3)_2$).

3e: IR (KBr): 3355 (N-H str.), 3130 (C-H str., Ar-H), 2180 (C≡N str.), 1520 (N-O str.), 1670 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 7.73-7.20 (m, 12H, Ar-H), 10.28 (s, 1H, NH of indole).

Synthesis of 8-[(1*N*-ethoxyphthalimido-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene) amino]-3,6-diphenyl-1,3,3*a*,9*a*-tetrahydro-6*H*-isoxazolo[3',4':4,5]-[1,3]thiazolo[3,2-*a*] pyridine-5,7-dicarbonitrile, 4a. Compound **3a** (0.01 mole, 5.28 g) was dissolved in 50 mL absolute ethanol and sodium hydride (0.01 mole) was added at 5-10ºC in small portion with constant stirring till effervescences ceases. Bromoethoxyphthalimide (0.01 mole, 2.70 g) in absolute ethanol was added to above mixture with constant stirring on a magnetic stirrer. The reaction mixture was further stirred for 3 hr more. Reaction mixture was slowly poured into crushed ice (50 g) with constant stirring. Solid obtained was filtered, washed and dried. Alternatively this reaction was carried out in presence

Table I — Physical and analytical characterization data for synthesized compounds

Compd	Mol. Formula	Mol. Wt.	Ar	Yield (%)	m.p. °C	Found (Calcd) % N
1a	$C_{22}H_{14}N_4OS$	382	C_6H_5	60	150	12.80(14.65)
1b	$C_{24}H_{18}N_4O_3S$	442	4-$OCH_3C_6H_5$	73	168	11.11(12.66)
1c	$C_{22}H_{12}Cl_2N_4OS$	452	4-ClC_6H_5	69	130	12.45(12.41)
1d	$C_{26}H_{24}N_6OS$	468	4-$N(CH_3)_2C_6H_5$	64	190	16.11(17.94)
1e	$C_{22}H_{12}N_4O_5S$	472	3-$NO_2C_6H_5$	74	110	15.65(17.79)
2a	$C_{22}H_{17}N_5OS$	399	C_6H_5	76	90	16.61(17.53)
2b	$C_{24}H_{21}N_5O_3S$	459	4-$OCH_3C_6H_5$	70	144	15.31(15.24)
2c	$C_{22}H_{15}Cl_2N_5OS$	469	4-ClC_6H_5	62	155	14.00(14.95)
2d	$C_{26}H_{27}N_7OS$	485	4-$N(CH_3)_2C_6H_5$	65	164	19.11(20.19)
2e	$C_{22}H_{15}N_7O_5S$	489	3-$NO_2C_6H_5$	62	70	18.30(20.03)
3a	$C_{30}H_{20}N_6O_2S$	528	C_6H_5	67	130	13.22(15.90)
3b	$C_{32}H_{24}N_6O_4S$	588	4-$OCH_3C_6H_5$	62	115	13.45(14.28)
3c	$C_{30}H_{18}Cl_2N_6O_2S$	598	4-ClC_6H_5	58	178	12.63(14.07)
3d	$C_{34}H_{30}N_8O_2S$	614	4-$N(CH_3)_2C_6H_5$	53	110	18.00(18.23)
3e	$C_{30}H_{18}N_8O_6S$	618	3-$NO_2C_6H_5$	60	95	17.58(18.11)
4a	$C_{40}H_{27}N_7O_5S$	717	C_6H_5	75	154	13.68(13.66)
4b	$C_{42}H_{31}N_7O_7S$	777	4-$OCH_3C_6H_5$	72	88	11.49(12.61)
4c	$C_{40}H_{25}Cl_2N_7O_5S$	787	4-ClC_6H_5	70	100	12.40(12.46)
4d	$C_{44}H_{37}N_9O_5S$	803	4-$N(CH_3)_2C_6H_5$	71	166	14.35(15.68)
4e	$C_{40}H_{25}N_9O_9S$	807	3-$NO_2C_6H_5$	70	132	14.89(15.61)
5a	$C_{29}H_{18}N_4O_2S$	486	C_6H_5	62	118	10.00(11.52)
5b	$C_{31}H_{22}N_4O_4S$	546	4-$OCH_3C_6H_5$	57	120	10.27(10.25)
5c	$C_{29}H_{16}Cl_2N_4O_2S$	556	4-ClC_6H_5	64	96	9.64(10.09)
5d	$C_{33}H_{28}N_6O_2S$	572	4-$N(CH_3)_2C_6H_5$	59	143	12.68(14.67)
5e	$C_{29}H_{16}N_6O_6S$	576	3-$NO_2C_6H_5$	57	140	13.98(14.58)
6a	$C_{29}H_{18}N_6OS$	498	C_6H_5	65	70	15.77(16.86)
6b	$C_{31}H_{22}N_6O_3S$	528	4-$OCH_3C_6H_5$	76	80	13.80(15.04)
6c	$C_{29}H_{16}Cl_2N_6OS$	568	4-ClC_6H_5	82	135	13.04(14.81)
6d	$C_{33}H_{28}N_8OS$	584	4-$N(CH_3)_2C_6H_5$	58	120	18.72(19.16)
6e	$C_{29}H_{16}N_8O_5S$	588	3-$NO_2C_6H_5$	62	165	17.99(19.04)
7a	$C_{39}H_{25}N_7O_4S$	687	C_6H_5	65	100	12.19(14.26)
7b	$C_{41}H_{29}N_7O_6S$	747	4-$OCH_3C_6H_5$	70	55	12.30(13.11)
7c	$C_{39}H_{23}Cl_2N_7O_4S$	757	4-ClC_6H_5	72	157	11.98(12.96)
7d	$C_{43}H_{35}N_9O_4S$	773	4-$N(CH_3)_2C_6H_5$	69	149	14.78(16.29)
7e	$C_{39}H_{23}N_9O_8S$	777	3-$NO_2C_6H_5$	66	133	15.58(16.21)

of pyridine as a base. Equivalent amount of **3a** and alkoxyphthalimide was refluxed in absolute alcohol using a calculated amount of pyridine for 20 hr. The cooled solution was filtered and the filtrate was concentrated under reduced pressure. On cooling, the solid obtained was filtered, washed and dried. Compound obtained by both the processes was purified by recrystallization from ethanol. It was observed that the yield was better in NaH process whereas quality of product was better in pyridine process. IR (KBr): 3160 (C-H str., Ar-H), 1640 (C=O str.), 2143 (C≡N str.), 1545 (N-O str.), 1090 cm^{-1} (C-O str.); ^1H NMR ($CDCl_3$): δ 7.85-7.40 (m, 18H, Ar-H), 4.28 (t, 2H, OCH_2), 3.49 (t, 2H, NCH_2).

Compounds **4b-e** were synthesized by similar method with minor modifications like reflux time, recrystallization solvent, *etc*. Their characteristic analytical data are mentioned in **Table I** and spectral data are given below.

4b: IR (KBr): 3054 (C-H str., Ar-H), 1085 (C-O str.), 2946 (C-H str., CH_3), 2130 (C≡N str.), 1560 (N-O str.), 1650 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 7.53-7.06 (m, 16H, Ar-H), 4.53 (t, 2H, OCH_2), 3.29 (t, 2H, NCH_2), 3.67 (s, 3H, OCH_3).

Table II — Results of antibacterial activity of synthesized compounds. Zone of inhibition of growth in mm (activity index)

Compd	*B. subtilis*	*E. coli*	*K. pneumoniae*	*P. aeruginosa*
3c	6(0.40)	5(0.31)	9(0.50)	9(0.52)
4a	7(0.46)	6(0.37)	10(0.55)	10(0.58)
4b	6(0.40)	4(0.25)	11(0.61)	10(0.58)
4c	11(0.73)	8(0.50)	16(0.88)	12(0.70)
4d	10(0.66)	7(0.43)	14(0.77)	11(0.64)
4e	9(0.60)	6(0.37)	14(0.77)	9(0.52)
6c	9(0.60)	6(0.37)	9(0.50)	9(0.52)
7a	10(0.66)	6(0.37)	10(0.55)	9(0.52)
7b	10(0.66)	5(0.31)	12(0.66)	10(0.58)
7c	12(0.80)	10(0.62)	15(0.83)	12(0.70)
7d	11(0.73)	8(0.50)	11(0.61)	11(0.64)
7e	9(0.60)	7(0.43)	9(0.50)	9(0.52)
Standard	15	16	18	17

4c: IR (KBr): 3170 (C-H str., Ar-H), 766 (C-Cl str.), 2188 (C≡N str.), 1580 (N-O str.), 1680 (C=O str.), 1090 cm^{-1} (C-O str.); ^1H NMR ($CDCl_3$): δ 7.59-7.33 (m, 16H, Ar-H), 4.38 (t, 2H, OCH_2), 3.42 (t, 2H, NCH_2).

4d: IR (KBr): 3084 (C-H str., Ar-H), 2952 (C-H str., CH_3), 2160 (C≡N str.), 1530 (N-O str.), 1640 (C=O str.), 1050 cm^{-1} (C-O str.); ^1H NMR ($CDCl_3$): δ 7.89-7.48 (m, 16H, Ar-H), 4.59 (s, 2H, OCH_2), 3.20 (s, 2H, NCH_2), 2.87 (s, 6H, $N(CH_3)_2$).

4e: IR (KBr): 3140 (C-H str., Ar-H), 2180 (C≡N str.), 1525 (N-O str.), 1695 (C=O str.), 1024 cm^{-1} (C-O str.); ^1H NMR ($CDCl_3$): δ 7.69-7.22 (m, 16H, Ar-H), 4.26 (t, 2H, OCH_2), 3.48 (t, 2H, NCH_2).

Synthesis of *N*-(6,8-dihydro-7-phenyl-3-oxo-2-(phenylmethylidene)-2,3-dihydro-7*H*-[1,3]thiazolo-[3,2-*a*]pyridine-5-yl)benzamide, 5a. Compound **1a** (0.01 mole, 3.82 g) was suspended in 20 mL dilute sodium hydroxide solution in a conical flask and to it benzoyl chloride (0.01 mole, mL) was added portion wise with constant shaking until the odour of benzoyl chloride disappeared. The solid benzoyl derivative was filtered, washed with a little cold water and purified by recrystallization from ethanol. IR (KBr): 3354 (N-H str.), 3076 (C-H str., Ar-H), 2156 (C≡N str.), 1710 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 7.95-7.40 (m, 15H, Ar-H), 8.27 (s, 1H, CONH), 6.23 (s, 1H, C=CHAr).

Similarly compounds **5b-e** were prepared by the minor change in reflux time. Their characteristic analytical data are mentioned in **Table I** and spectral data are given below.

5b: IR (KBr): 3337 (N-H str.), 3144 (C-H str., Ar-H), 2170 (C≡N str.), 1087 (C-O str.), 2960 (C-H str., CH_3), 1675 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 7.68-7.34 (m, 13H, Ar-H), 8.10 (s, 1H, CONH), 3.66 (s, 3H, OCH_3), 6.30 (s, 1H, C=CHAr).

5c: IR (KBr): 3355 (N-H str.), 3154 (C-H str., Ar-H), 2120 (C≡N str.), 790 (C-Cl str.), 1664 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 7.62-7.26 (m, 13H, Ar-H), 8.45 (s, 1H, CONH), 6.28 (s, 1H, C=CHAr).

5d: IR (KBr): 3338 (N-H str.), 3110 (C-H str., Ar-H), 2173 (C≡N str.), 2940 (C-H str., CH_3), 1700 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 7.78-7.35 (m, 13H, Ar-H), 8.34 (s, 1H, CONH), 2.83 (s, 6H, $N(CH_3)_2$), 6.32 (s, 1H, C=CHAr).

5e: IR (KBr): 3355 (N-H str.), 3085 (C-H str., Ar-H), 2144 (C≡N str.), 1540 (N-O str.), 1690 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 7.65-7.08 (m, 13H, Ar-H), 8.03 (s, 1H, CONH), 6.26 (s, 1H, C=CHAr).

Synthesis of *N*-(5,7-dicyano-3,6-diphenyl-2*H*, 6*H*-pyrazolo[3',4':4,5][1,3]thiazolo[3,2-*a*]pyridine-8-yl)benzamide, 6a. Hydrazine hydrate (0.02 mole, 0.90 mL) and compound **5a** (0.01 mole, 5.46 g) were refluxed in ethanol for 6 hr. The reaction mixture was cooled and filtered. Filtrate was poured into crushed ice, resultant solid was washed with cold water, dried and purified by recrystallization from ethanol. IR (KBr): 3370 (N-H str.), 3125 (C-H str., Ar-H), 2155 (C≡N str.), 1705 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 7.72-7.30 (m, 15H, Ar-H), 8.34 (s, 1H, CONH), 7.93 (s, 1H, NH of pyrazole).

Likely compounds **6b-e** were synthesized with minor change in reaction conditions. Their characteristic analytical data are mentioned in **Table I** and spectral data are given below.

6b: IR (KBr): 3355 (N-H str.), 3050 (C-H str., Ar-H), 2110 (C≡N str.), 1060 (C-O str.), 2946 (C-H str., CH_3), 1654 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 7.64-7.32 (m, 13H, Ar-H), 8.44 (s, 1H, CONH), 3.60 (s, 3H, OCH_3), 7.87 (s, 1H, NH of pyrazole).

6c: IR (KBr): 3335 (N-H str.), 3048 (C-H str., Ar-H), 2180 (C≡N str.), 762 (C-Cl str.), 1682 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 7.68-7.36 (m, 13H, Ar-H), 8.22 (s, 1H, CONH), 7.82 (s, 1H, NH of pyrazole).

6d: IR (KBr): 3390 (N-H str.), 3160 (C-H str., Ar-H), 2115 (C≡N str.), 2964 (C-H str., CH_3), 1640 cm^{-1} (C=O str.); ^1H NMR ($CDCl_3$): δ 7.85-7.42 (m, 13H, Ar-H), 8.61 (s, 1H, CONH), 2.80 (s, 6H, $N(CH_3)_2$), 7.91 (s, 1H, NH of pyrazole).

6e: IR (KBr): 3382 (N-H str.), 3144 (C-H str., Ar-H), 2134 (C≡N str.), 1556 (N-O str.), 1655 cm^{-1} (C=O

str.); ^{1}H NMR ($CDCl_3$): δ 7.92-7.53 (m, 13H, Ar-H), 8.14 (s, 1H, CONH), 7.86 (s, 1H, NH of pyrazole).

Synthesis of *N*-(5,7-dicyano-3,6-diphenyl-2*N*-ethoxyphthalimido-2*H*,6*H*-pyrazolo[3',4':4,5][1,3]-thiazolo[3,2-*a*]pyridine-8-yl)benzamide, 7a. To a mixture of compound **6a** (0.01 mole, 4.98 g) and bromoethoxyphthalimide (0.01 mole, 2.70 g) in absolute ethanol, pyridine was added as a base. The reaction mixture was then refluxed for 22 hr. The solvent was evaporated under reduced pressure to concentrate the contents and subsequently cooled. Crystals of pyridinium bromide were filtered while hot and the filtrate was kept at RT overnight. Crystals separated were filtered and dried. Alternatively sodium hydride process (*vide supra* **4a**) was also used. In this process the solid obtained was not crystalline but the yields were better. Both the products were recrystallised from alcohol. IR (KBr): 3366 (N-H str.), 3110 (C-H str., Ar-H), 2184 (C≡N str.), 1695 (C=O str.), 1035 (C-O str.), 1560 cm^{-1} (N-O str.); ^{1}H NMR ($CDCl_3$): δ 7.72-7.30 (m, 19H, Ar-H), 8.14 (s, 1H, CONH), 4.52 (t, 2H, OCH_2), 3.28 (t, 2H, NCH_2).

Compounds **7b-e** were synthesized by similar method with minor modifications like reflux time, recrystallization solvent, *etc*. Their characteristic analytical data are mentioned in **Table I** and spectral data are given below.

7b: IR (KBr): 3340 (N-H str.), 3045 (C-H str., Ar-H), 2120 (C≡N str.), 1044 (C-O str.), 2950 (C-H str., CH_3), 1730 (C=O str.), 1580 cm^{-1} (N-O str.); ^{1}H NMR ($CDCl_3$): δ 7.77-7.32 (m, 17H, Ar-H), 8.20 (s, 1H, CONH), 3.62 (s, 3H, OCH_3), 4.63 (t, 2H, OCH_2), 3.38 (t, 2H, NCH_2).

7c: IR (KBr): 3320 (N-H str.), 3088 (C-H str., Ar-H), 2180 (C≡N str.), 752 (C-Cl str.), 1625 (C=O str.), 1085 (C-O str.), 1534 cm^{-1} (N-O str.); ^{1}H NMR ($CDCl_3$): δ 7.86-7.42 (m, 17H, Ar-H), 8.50 (s, 1H, CONH), 4.50 (t, 2H, OCH_2), 3.32 (t, 2H, NCH_2).

7d: IR (KBr): 3352 (N-H str.), 3105 (C-H str., Ar-H), 2118 (C≡N str.), 2958 (C-H str., CH_3), 1680 (C=O str.), 1020 (C-O str.), 1542 cm^{-1} (N-O str.); ^{1}H NMR ($CDCl_3$): δ 7.60-7.27 (m, 17H, Ar-H), 8.53 (s, 1H, CONH), 2.84 (s, 6H, $N(CH_3)_2$), 4.67 (t, 2H, OCH_2), 3.39 (t, 2H, NCH_2).

7e: IR (KBr): 3315 (N-H str.), 3135 (C-H str., Ar-H), 2160 (C≡N str.), 1550 (N-O str.), 1687 (C=O str.), 1055 cm^{-1} (C-O str.); ^{1}H NMR ($CDCl_3$): δ 7.68-7.35 (m, 17H, Ar-H), 8.40 (s, 1H, CONH), 4.58 (t, 2H, OCH_2), 3.22 (t, 2H, NCH_2).

Antibacterial activity

Twelve compounds were screened for antibacterial activity using disc diffusion method. The antibacterial activity of synthesized compounds was tested against *Escherichia coli*, *Bacillus subtilis*, *Klebsilla pneumoniae* and *Pseudomonas aeruginosa* using a nutrient agar medium. It consists of peptone (1%), NaCl (0.5%) and beef extract (1%). All the ingredients were dissolved in distilled water and the *p*H adjusted as per optimum requirement. 2% Agar-agar solution was added and the medium was sterilized. Paper discs which consisted of small discs of standard filter paper were impregnated with a given quantity of compound (500 ppm). They were placed on Petri plates of culture media and inoculated with the organism to be tested. After inoculation, degree of sensitivity was determined by measuring the visible area (arc method) of inhibition of growth into the surrounding media. The results are presented in **Table II**.

Conclusions

The synthesized compounds show weak to stronger activity. Activity of compounds increases when chloro group is present at the *para* position of the aryl ring of the molecule. Thus **4c** and **7c** having Cl group show stronger activity than the other compounds. Alkoxyphthalimide group when present in the molecule enhances its antibacterial activity. Compounds **3c** and **6c** which do not have alkoxyphthalimide pharmacophore show weaker activity than the other compounds of the series which contain this moiety. These compounds show comparatively stronger activity against *K. pneumoniae*, and moderate activity against *B. subtilis* and *P. aeruginosa*. Overall, activity is weak against *E. coli*. It may be emphasized that molecules containing indolyl nucleus attached to the tricyclic system show better activity than compounds in which it is not present.

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References

1 Gad-Elkareem M A M, Fatlah A M A & Elneairy M A A, *Phosphorus Sulfur Silicon*, 181, **2006**, 891.
2 Liang J C, Yeh J L, Wang C S, Liou S F, Tsai C H & Chen I J, *Bioorg Med Chem*, 10(3), **2002**, 719.
3 Tasaka S, Ohmori H, Gomi N, Lion M, Machida T, Kiue A, Naito S & Kuwano M, *Bioorg Med Chem Lett*, 11(2), **2001**, 275.
4 Shah A, Gevariya H, Motohashi N, Kawase M, Fakas S, Gyorgyi G & Molnar J, *Int J Antimicrob Agents*, 20, **2002**, 227.
5 Penning T D, Talley J J, Bertenshaw S R, Carter J S, Collins P W, Docter S, Graneto M J, Lee L F, Malecha J W, Miyashiro J M, Rogers R S, Rogier D J, Yu S S, Andreson G D, Burton E G, Cogburn J N, Gregory S A, Koboldt C M, Perkins W E, Seibert K, Veenhuizen A W, Zhang Y Y & Isakson P C, *J Med Chem*, 40, **1997**, 1347.
6 Terrett N K, Bell A S, Brown D & Ellis P, *Bioorg Med Chem Lett*, 6, **1996**, 1819.
7 Elguero J, Goya P, Jagerovic N & Silva A M S, *Targets Heterocycl Syst*, 6, **2002**, 52.
8 El-Galil A, Ahmed N, Latif A & Abdalla M M, *Acta Pharm*, 56, **2006**, 203.
9 Imaizumi K & Sado T, *JP* 0680570, **1994**; *Chem Abstr*, 121, **1994**, 91797.
10 Akbas E, Berber I, Sener A & Hasanov B, *Il Farmaco*, 60, **2008**, 23.
11 Masevicius V, Juskenas R & Tumkevicius S, *Chem Heterocycl Comp*, 43, **2007**, 12.
12 Dasai N C, Shah M D, Bhavsar A M & Saxena A K, *Indian J Chem*, 47B, **2008**, 1135.
13 Brile D, Aurich R & Egerland U, *Unerferth K Pharmazine*, 60, **2005**, 732.
14 Ryan A J, Welling P G & Wright S E, *Food Cosmet Toxicol*, 7, **2002**, 287.
15 Ahn J H, Kim H M, Jung S H, Kang S K, Kim K R, Rhee S D, Yong S D, Cheon H G & Kim S S, *Bioorg Med Chem Lett*, 14, **2004**, 4461.
16 Kumar A, Kumar G & Kapoor M, *Synth Commun*, 36, **2006**, 215.
17 Patterson J W, Cheung P S & Ernest M J, *J Med Chem*, 35, **1992**, 507.
18 Dannhardt G, Kiefer W, Kramer G, Maehrlein S, Nowe U & Fiebich B, *Eur J Med Chem*, 35, **2000**, 499.
19 Jayashankara B & Lokanatha K M, *ARKIVOC*, xi, **2008**, 75.
20 Smietana M, Gouverneur V & Mioskowski C, *Tetrahedron Lett*, 40, **1999**, 1291.
21 Aeillo E, Aeillo S, Mingoia F, Bacchi A, Pelizzi G, Musiu C, Setzu M, Pani A, La-Colla P & Marongiu M, *Bioorg Med Chem*, 8(12), **2000**, 2719.
22 Rajanarendar E, Karunakar D & Srinivas M, *Indian J Chem*, 43B, **2004**, 643.
23 Goda F E, Maarouf A R & El-Bendary E R, *Sandi Pharm J*, 11(3), **2007**, 111.
24 Coutouli-Argyropoulou E, Lianis P, Mitakou M, Giannoulis A & Nowak J, *Tetrahedron*, 62, **2006**, 1494.
25 Inoue H, Konda M, Hashiyama T, Otsuka H, Takahashi K, Gaino M, Date T, Aloe K, Takeo M, Murata S, Narita H & Nagao T, *J Med Chem*, 34, **1991**, 675.
26 Soni A K, Krupadanam G L D & Srimannarayana G, *ARKIVOC*, xvi, **2006**, 35.
27 Basappa, Mantelingu K, Sadashiva M P & Rangappa K S, *Indian J Chem*, 43B, **2004**, 1954.
28 Benltifa M, Vidal S, Gueyrard D, Goekjian P G, Msaddek M & Praly J P, *Tetrahedron Lett*, 47, **2006**, 6143.
29 Markourtz J S, Brown C S & More T R, *Ann Pharma Cotha*, 33, **1999**, 73; *Chem Abstr*, 130, **1999**, 332728.
30 Quan M L, Liquw A Y, El-Ls-Christopher D, Pruitty J R, Carini D S, Bostrom L, Harrison K & Knabb R M, *J Med Chem*, 42, **1999**, 2752; *Chem Abstr*, 131, **1999**, 170287.
31 Epple R, Russo R, Azimioara M, Cow C, Xie Y, Wang X, Wityak J, Karanewsky D, Gerken A, Iskandar M, Saez E, Seidel H M & Tian S S, *Bioorg Med Chem Lett*, 16, **2006**, 4376.
32 Sharma R, Nagda D P & Talesara G L, *ARKIVOC*, i, **2006**, 1.
33 Ure J A & Perassalo M, *J Neuro Sci*, 1, **2000**, 177.
34 Singh B, Mehta D, Baregama L K & Talesara G L, *Indian J Chem*, 43B, **2004**, 1306.
35 Abdel-Gawad S M, El-Gaby M S A & Ghorab M M, *Il Farmaco*, 55, **2000**, 249.