INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Research Article

MICROWAVE ASSISTED SYNTHESIS OF SOME 2-[(SUBSTITUTED BENZYLIDENE) IMINO]-3-(N-CYCLOHEXL CARBOXAMIDO)-4, 5-DI SUBSTITUTED THIOPHENES

Rekha Parmesh[1]*, Lohitha P[1] and Saravanan J[2]

[1]Department of Pharmaceutical Chemistry, The Oxford College of Pharmacy, Hongasandra, Begur Road, Bangalore, Karnataka, India.
[2]Department of Pharmaceutical Chemistry, The PES College of Pharmacy, Hanumanthanagar, Bangalore, Karnataka, India.

ABSTRACT

In this present work, a series of new 2-[(substituted benzylidene) imino]-3-(N-cyclohexl carboxamido)-4,5-di substituted thiophenes were synthesized in a multi step method and its structure has been elucidated by elemental analysis and spectral tools.. In the first step N-cyclohexyl cyano acetamide MSR-5 was synthesized by the condensation of Cyclohexylamine and Ethyl cyano acetate. Reaction of compound MSR-5 with methylenic ketone using ammonium acetate and glacial acetic acid as an acidic catalyst was carried out by refluxation in benzene for 8hrs by employing Dean Stark apparatus afforded 2-Cyano –2- (alkylidene)-N-cyclohexyl carboxamides [I]. Compound [I] represents the important key intermediate from which all the new target polysubstituted thiophenes were synthesized thus compound [2] was introduced in reaction by dissolving in alcohol react with elemental sulfur in the presence of basic catalyst, diethyl amine in ethanol to form 2-amino-3-(cyclohexyl carboxamido)-4,5-di substituted thiophenes MSR-11 & 12. In the final step a new series of compounds were synthesized from 2-amino-3-N-cyclohexyl carboxamido-4,5-disubstituted thiophenes (MSR-11&12) by heating in a microwave oven with various substituted aromatic aldehydes in isopropyl alcohol with glacial acetic acid as a catalyst to yield 2-[(substituted benzylidene) imino]-3-(N-cyclohexl carboxamido)-4,5-disustituted thiophenes MSR-11a-11k & MSR-12a-12k.

Keywords: N-cyclohexyl cyano acetamide, 2-Cyano–2-(alkylidene)-N-cyclohexyl carboxamides, 2-[(substituted benzylidene) imino]-3-(N-cyclohexl carboxamido)-4,5-disustituted thiophenes.

INTRODUCTION

Generally many drugs are obtained from plants and animals, but most drugs used in modern medicine are products of advances in synthetic organic chemistry and biotechnology. For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry.

Heterocycles often seemed to be perfect bioisosteres according to they can delivery equal or even better biological efficacy through their similarity in structural shape and electronic distribution[1].

Heterocycles play an important role in biological process because the side group of the most typical and essential constituents of living cells; The DNA and RNA are based on aromatic heterocycles. Among the 20 million chemical compounds identified by the end of the second millennium, more than two third are fully or partially aromatic

and approximately half are heterocyclic, so we have chosen the heterocyclic compound "THIOPHENE".

The recent improvement in the knowledge of the mechanism of action of the available drug in the biochemical mechanism of resistance to them may be used as a basis for designing new and better action against diseases[2]. Published literature and articles are considered the evidence of the interest shown in the synthesis and characterization of thiophene compounds in search of potential drugs.

Microwave irradiation was recognized in the mid-1980s to be an efficient heating source for chemical reactions, where reactions that require several hours under conventional conditions can often be completed in a few minutes with very high yields and reaction selectivities. Many reports have been published on the beneficial effect of microwave irradiation in organic synthesis, e.g., for the preparation of heterocycles and for organometallic and rearrangement reactions. A number of review articles have appeared that cover the underlying theory of microwave dielectric heating, the relevant dielectric parameters, and microwave-assisted organic reactions[3].

Generally many drugs are obtained from plants and animals, but most drugs used in modern medicine are products of advances in synthetic organic chemistry and biotechnology. For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry.

Various thiophenes have been reported for their biological and pharmacological activities such as antimicrobial[4, 10], antifungal[5], anti tubercular[6], anti tumor[7], antimycobacterial[8],anti proliferative[9], antibacterial[11, 12], antiviral, anti protozoal, herbicidal, anti ulcer, CNS depressant & anticonvulsant[13], analgesic, anti inflammatory activites[14] and so on

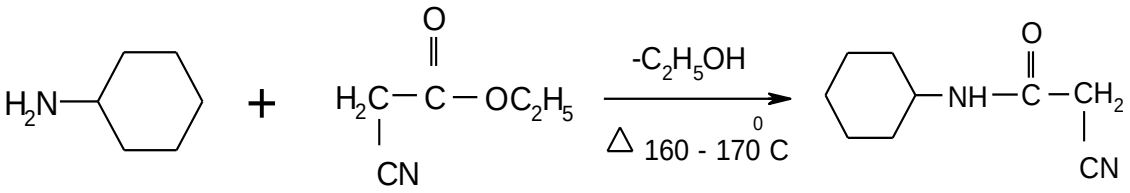
The appreciation of thiophene derived heterocyclic compounds diverse biological applications and the continuous application of thiophene derivatives as synthons in organic synthesis, has led to the synthesis of thiophene analogues and their subsequent heterocyclics.

In view of these observations and their increasing importance in pharmaceutical and biological field, it was considered of interest to synthesize some new chemical entities incorporating the molecular frame work and to evaluate their biological activities.

MATERIAL AND METHODS

Synthetic procedure for the preparation of N-cyclohexylcyanoacetamide [MSR-5]:

A mixture of Cycloheylamine (0.5 M) and ethyl cyano acetate (56.5 ml; 0.5 M) was taken in a conical flask and heated on mantle for 3-4 hrs at 160- 170°C. Then the reaction mixture was transferred into a beaker and kept at room temperature for over night. The solid obtained was washed with ethanol, dried & recrystallized by ethanol.



Cyclohexylamine **Ethyl cyano acetate** **MSR-5**
N-cyclohexyl cyano acetamide

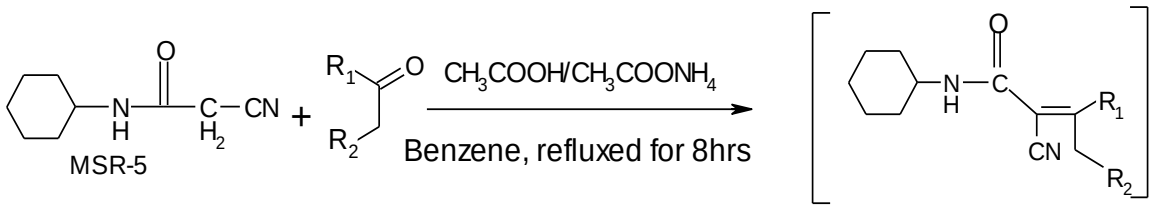
Step-I

Synthetic procedure for the preparation of 2-cyano-2-alkylidene-N-cyclohexyl carboxamides [I] (Step-II)

A mixture of cyclohexyl cyano acetamide [MSR-5] (0.04 M), appropriate methylenic ketones (0.04 M), (cyclohexanone and cycloheptanone), ammonium acetate (2 g) and glacial acetic acid (2 ml) in benzen(e (100 ml) was refluxed with an arrangement for continuous separation of water involving dean stark apparatus. After 8 hrs the reaction mixture was cooled, diluted with 10 ml benzene and washed successively with sodium carbonate solution (10% w/v in water) and water. Dried over anhydrous sodium sulphate. The solvent was removed under vacuum and the intermediate crude product obtained was immediately processed for next step.

Synthetic procedure for the preparation of 2-amino-3-(cyclohexyl carboxamido)-4,5-di substituted thiophenes MSR-11 & 12 (Step - III)

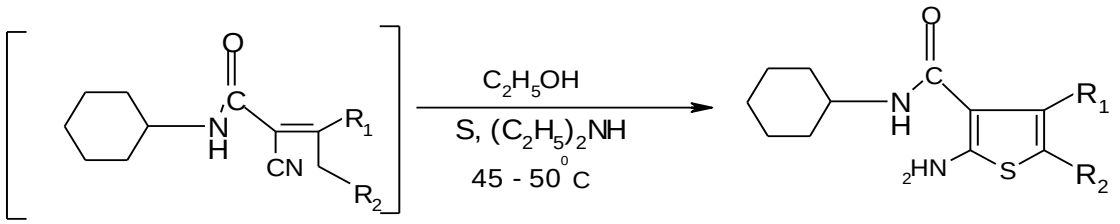
The intermediate obtained from the previous step dissolved in alcohol (30 ml) sulphur(1.28g; 0.04M) was added with stirring by maintaining the temperature between 45-50ºC during addition. To the reaction mixture, diethyl amine (6.0 ml) was added drop wise the stirring was continued for 1hr at 45-50ºC and chilled over night. The solid obtained was filtered, washed with ethanol and crystallized from ethanol.



(MSR- 5) **Methylenic ketone** **2-Cyano –2- (alkylidene)-N-cyclohexyl carboxamides [I]**

Where: R_1, R_2 = - $(CH_2)_4$-, - $(CH_2)_5$-.

Step-II



2-Cyano –2-(alkylidene)-N-Cyclohexylcarboxamides [I]

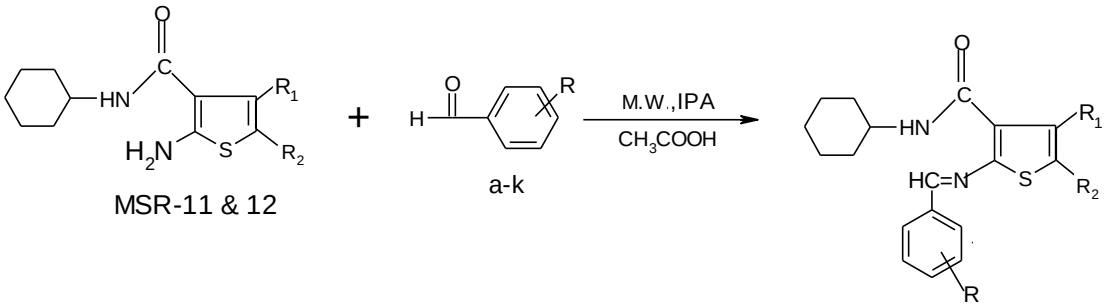
2–amino–3–N- Benzyl Carboxamido –4,5-disubstituted thiophenes (MSR 11 & 12)

Where: R_1, R_2 = - CH_3, - $(CH_2)_3$-.

Step-III

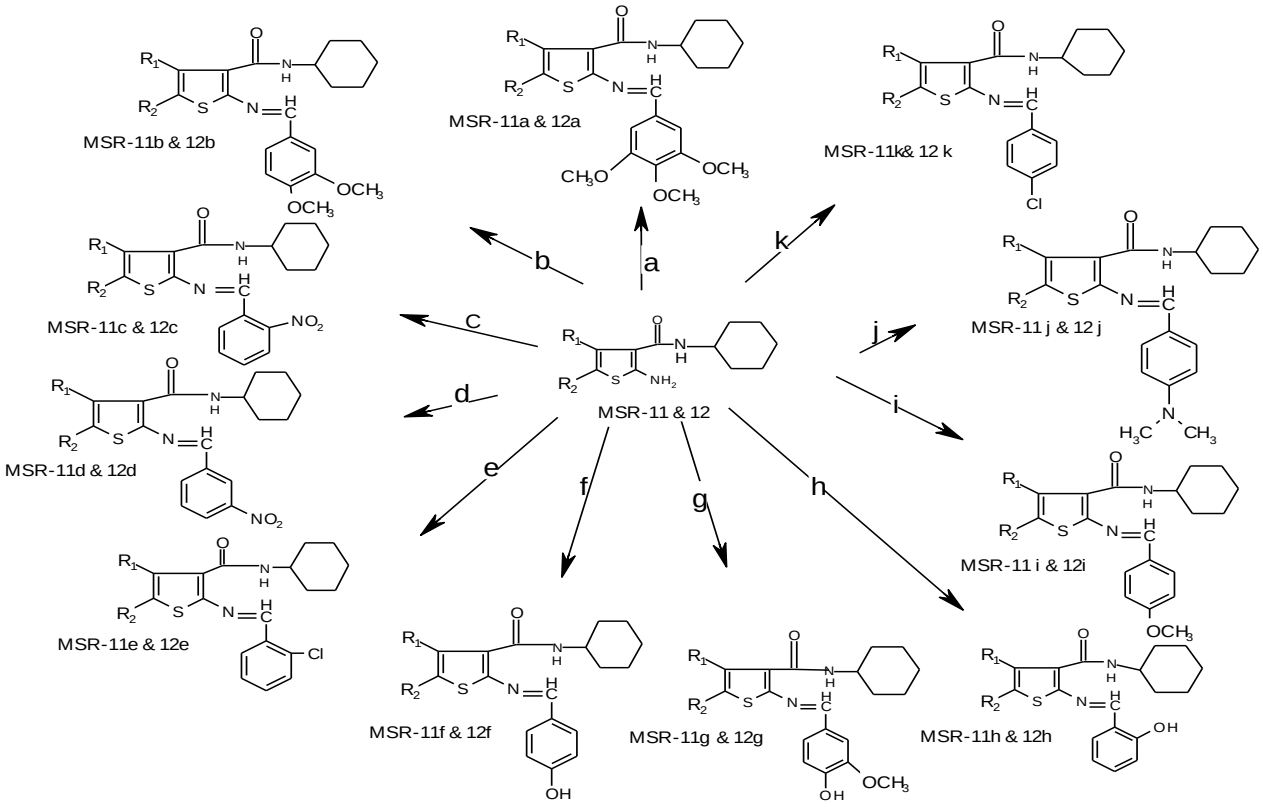
Microwave assisted synthetic procedure for the preparation of 2-[(substituted benzylidene) imino]-3-(N-cyclohexyl carboxamido)-4,5-di substituted thiophenes MSR11a-11k & MSR 12a-12k

A mixture of the starting compounds (MSR-11 & 12) (0.005 M) and the required aryl aldehydes (0.005 M) in isopropyl alcohol (30 ml) and catalytic amount of glacial acetic acid (2 ml) was taken into a conical flask and subjected to microwave irradiation for 30 seconds. The mixture was cooled to room temperature, the solid separated was filtered, washed with isopropyl alcohol and recrystallised with DMF: Water mixture (5:1).



2-amino-3-(cyclohexyl carboxamido) 4,5-di substituted thiophenes **Various aromatic aldehydes** **MSR11a-11k & MSR 12a-12k,**

Where: R_1, R_2 = - CH_3, - $(CH_2)_3$-.



SCHEME

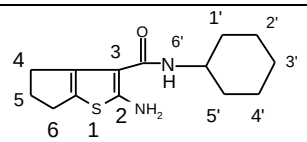
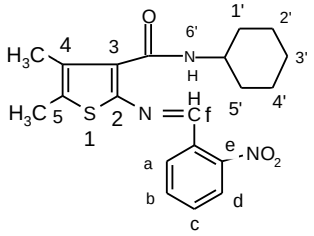
Substitution	Compound No	M.P °C
a = 3,4,5-Trimethoxy benzaldehyde	(MSR-11a & 12a)	101
b =3,4-Dimethoxy benzaldehyde	(MSR-11b& 12b)	112
c =2-Nitro benzaldehyde	(MSR-11c& 12c)	132
d =3-Nitro benzaldehyde	(MSR-11d& 12d)	102
e= 2-Chloro benzaldehyde	(MSR-11e & 12e)	115
f= 4-Hydroxy benzaldehyde	(MSR-11f& 12f)	117
g=4-Hydroxy-3-methoxy benzaldehyde	(MSR-11g & 12g)	113
h = 2-Hydroxy benzaldehyde	(MSR-11h & 12h)	126
i = 4-Methoxy benzaldehyde	(MSR-11i & 12i)	158
j = 4-Dimethyl amino benzaldehyde	(MSR-11j & 12j)	124
k = 4-Chloro benzaldehyde	(MSR-11k& 12k)	103

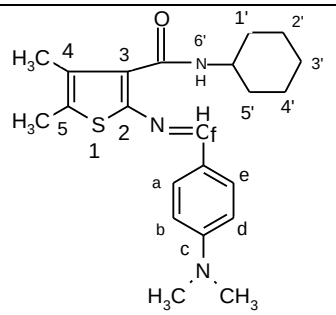
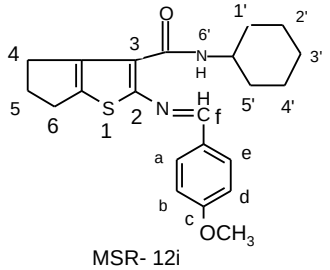
RESULTS AND DISCUSSION

The formation of the parent compounds MSR 11& 12 were confirmed by Lassingnes test, TLC, UV and IR spectra. The IR spectra exhibit a distinct peak at 3230-3375 cm^{-1} (NH_2 group), 3293 cm^{-1}(-NH);1652-1679cm^{-1}(C=O);3150-3050cm^{-1}(Ar-CH);2940-2800cm^{-1}(Ali-CH); 1545-1570cm^{-1}(Ar-C=C);705.56 (S-C); Confirms the formation of 2-amino-3-(cyclohexyl carboxamido)-4,5-di substituted thiophenes MSR-11 & 12.

The formation of the title compounds MSR 11a-11k & MSR 12a-12k were preliminarily confirmed by the difference in MP, Rf value, UV spectra (bathochromic shift), and specific IR peak where there is an absence of the primary aromatic amino peak at 3230-3375 cm^{-1} in MSR-11 & 12 and an appearance of a new peak at 1550-1560 cm^{-1} for -N=CH- (imine) and disappearence of amino peak in the title compounds & specific absorption peaks for other groups like $–NO_2$, -Cl, $-CH_3$, $-OCH_3$ etc. itself is sufficient to explain the formation of the new compounds.

TABLE-I: SPECTRAL DATA

Comp No	Structure	^{1}H NMR ($CDCl_3$)
12	 MSR-12	5.66 (s, 1H, -NH-, 6'); 5.02 (b, 2H, $-NH_2$,2); 3.07 (t, 2H, $-CH_2$-, 1'); 2.99(t, 2H, $-CH_2$-,5'); 1.24-1.98 (m, 12H, $-CH_2$-, 2', 3' 4' 4,5,6).
11c	 MSR-11c	7.9 (s, 1H, -N=CH-, f); 7.49 (m, 2H, Ar-H, a,d); 7.03 (m, 2H, Ar-H,b,c);4.56 (s, 1H, -NH,7'); 3.87 (s, 6H, $-CH_3$, 4,5); 3.45 (t, 2H, $-CH_2$-, 5'); 2.99(t, 2H, $-CH_2$-,1'); 1.50-2.02 (m, 4H, $-CH_2$-, 2'4').

11j	 MSR-11 j	7.9 (s, 1H, -N=CH-, f); 7.49 (d, 2H, Ar-H, b,d); 7.08 (d, 2H, Ar-H,a,e); 3.87 (s, 6H, -N-{CH_3}$_2$,c); 2.56 (s, 6H, -CH_3, 4,5); 2.0(s, 2H, -CH_2-,1'); 1.5 (t, 4H, -CH_2-, 5',4'); 1.02 (t, 4H, -CH_2-, 2',3').
12i	 MSR- 12i	8.55(s, 1H, -N=CH-, f); 7.49 (d, 2H, Ar-H,b,d); 6.98 (d, 2H, Ar-H,a,e);5.42(s,1H, -NH,7'); 3.97 (s, 3H, -OCH_3); 2.64-2.98 (m, 6H, -CH_2-, 1',5',6);1.61-1.92(t, 10H, -CH_2-,2',3',4',4,5).

CONCLUSION

Based upon the fact, the present investigation was planned and considerable interest has been shown in the synthesis of 2-amino-3-(cyclohexyl carboxamido)-4,5-di substituted thiophenes (MSR-11 & 12) by Gewald reaction.

A new series of title compounds were synthesized from 2-amino-3-(cyclohexyl carboxamido)-4,5-di substituted thiophenes (MSR-11 & 12) by heating in a microwave oven with various substituted aromatic aldehydes in isopropyl alcohol with glacial acetic acid as a catalyst to yield MSR 11a-11k & MSR 12a-12k.

The new series of title compounds synthesized were confirmed preliminarily by M.P, TLC and spectral analysis (UV, IR) and then by NMR and Mass spectra.

ACKNOWLEDGEMENTS

The author is thankful to Management, The PES College of Pharmacy and The Oxford College of Pharmacy for giving the opportunity to work and necessary facilities. We are thankful to IISC, Bangalore, India for spectral analysis.

REFERENCES

1. Naoto Uramaru et al. Synthesis and Evaluation of in Vitro Bioactivity for Polysubstituted N-Arylpyrazole derivatives. Arab J Chem online. 2014.
2. Shashikant R Pattan et al. Synthesis of N-3(4-(4-chlorophenylthiazole-2-yl)-(2-(amino)methyl)-quinazoline-4(3H)-one and their derivatives for antitubercular activity. Ind J of Chem. 2006;45B:1778-81.
3. Shan-Shan Lin et al. Microwave-assisted enzyme-catalyzed reactions in various solvent systems. J Am Soc Mass spectrum. 2005;16:581–8.
4. Gouda MA, Berghot MA, El-Ghani GEA and Khalil AM. Synthesis and antimicrobial activities of some new thiazole and pyrazole derivatives based on 4,5,6,7-tetrahydrobenzothiophene moiety. Eur J Med Chem. 2010:1–8.
5. Pinto E, Queiroz MJRP, Vale-Silva LA, Oliveira JF, Begouin A, Begouin JM et al. Antifungal activity of synthetic di(hetero)arylamines based on the benzo[b]thiophene moiety. Bioorg Med Chem. 2008;16:8172–7.
6. Xiaoyun et al. Design, synthesis and anti-tubercular evaluation of new 2-acylated and 2-alkylated amino-5-(4-(benzyloxy)phenyl)thiophene-3-carboxylic acid derivatives. Eur J Med Chem. 2011;46(9):3551-63.
7. Romeo Romagnoli et al. Design, synthesis and biological evaluation of 3,5-

disubstituted 2-amino thiophene derivatives as a novel class of antitumor agents. Bioorg Med Chem. 2014;22:5097-109.
8. Radhika Nallangi et al. Development of antimycobacterial tetrahydrothieno[2,3-c]pyridine-3-carboxamides and hexahydrocycloocta[b]thiophene-3-carboxamides: Molecular modification from known antimycobacterial lead. Eur J Med Chem. 2014;76(9):110-7.
9. Nikolay S. Ilyinsky et al. Novel multi-targeting anthra[2,3-*b*]thiophene-5,10-diones with guanidine-containing side chains: Interaction with telomeric G-quadruplex, inhibition of telomerase and topoisomerase I and cytotoxic properties. Eur J Med Chem. 2014;85(6):605-14.
10. Pravin Kumar N et al. An efficient one-pot three-component synthesis and antimicrobial evaluation of tetra substituted thiophene derivatives. Chin Chem Lett. 2014;25(7):1099-103.
11. Li Zhang et al. Thiophene acetylenes and furanosesquiterpenes from *Xanthopappus subacaulis* and their antibacterial activities. Phy Chem. 2014;106:134-40.
12. Sara Tehranchian, TahminehAkbarzadeh, Mohammad Reza Fazeli, Hossein Jamalifar and Abbas Shafiee. Synthesis and antibacterial activity of 1-[1,2,4-triazol-3-yl] and 1-[1,3,4-thiadiazol-2-yl]-3-methylthio-6,7-dihydro-benzo[*c*] thiophen-4[5H]ones. Bioorg Med ChemLett. 2005;15:1023-25.
13. Jatava V, Mishra P, Kashawa S, and Stablesb JP. CNS depressant and anticonvulsant activities of some novel 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones Eur J Med Chem. 2008;43(9):1945-54.
14. Ajay D Pillai, Parendu D Rathod, Franklin P Xavier, Kamala K Vasu, Harish Padh, Vasudevan Sudarsanam et al. Design, synthesis and pharmacological evaluation of some 2-[4-morphplino]-3aryl-5-substituted thiophenes as novel anti-inflammatory agents: generation of a novel anti-inflammatory pharmacophore. Bioorg Med ChemLett. 2004;12:4667-71.