Synthesis and Biological Evaluation of 1,3-Diarylpyrazoles: *in vitro* Cytotoxicity Studies on Human Melanoma Cancer Cells

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Abstract

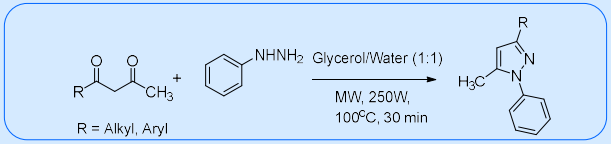
A large number of synthetic heterocyclic compounds are predominant among all types of pharmaceuticals, agrochemicals, veterinary products. This high significance of heterocycles is mainly because of their ability to involve in an extraordinarily wide range of reaction types. We have developed two alternate approaches for 1,3-diaryl pyrazoles i.e. microwave assisted and metal catalyzed approaches. We have initially developed an efficient microwave assisted synthetic approach by optimizing the reaction conditions such as solvent, microwave power and reaction time. A series of pyrazole compounds were prepared using arylhydrazines and dicarbonyl compounds. All the synthesized compounds were characterized by IR, 1H NMR, 13C NMR, and GC-MS analysis and evaluated for in vitro anticancer activity against human melanoma (A375 and SK-Mel-28) cancer cells. Pre-treatment with all compounds exhibited significant decrease in cell growth/viability.

Significance of Project

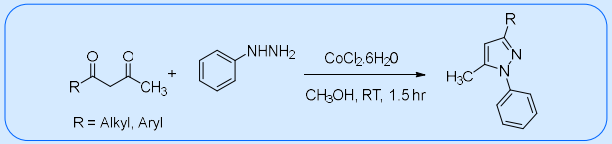
- The substituted pyrazoles with aromatic and heteroaromatic groups possess numerous biological activities, which makes them particularly interesting drug discovery research
- The existing methods suffered with some drawbacks such as longer reaction times, undesired products formation, and thus difficulty in product isolation and purification.
- Skin cancers are high-risk and aggressive type of cancer which exist in two major form: melanoma and non- melanoma.
- Non-melanoma Skin cancers (NMSCs) including Basal Cell Carcinoma(BCC) and Squamous Cell Carcinoma (SCC) are the most common type of cancer which comprises more than 1/3rd of all cancer in United states.
- Based on screening results, we are currently working on developing a new library of similar compounds while introducing new substituents to improve biological activity.

Results and Discussion

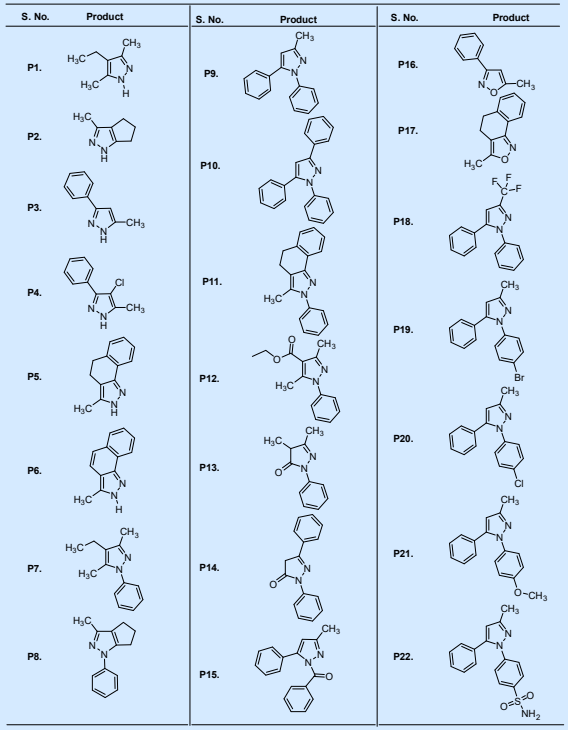
Microwave Assisted Synthesis of Substituted Pyrazoles



Catalytic Synthesis of Substituted Pyrazoles



S. No.	Catalyst	Solvent	% yield	S. No.	Catalyst	Solvent	% yield
1	$Ni^{II}Cl_2$	CH_3CN	53	7	$Cu^{II}(OTf)_2$	CH_3CN	94
2	$Ni^{II}(OTf)_2$	CH_3CN	43	8	No catalyst	CH_3CN	11
3	$Ni^{II}(acac)_2$	CH_3CN	69	9	$Co^{II}Cl_2.6H_2O$	CH_2Cl_2	94
4	$Co^{II}Cl_2.6H_20$	CH_3CN	~100	10	$Co^{II}Cl_2.6H_2O$	Dioxane	86
5	$Co^{II}SO_4$	CH_3CN	94	11	$Co^{II}Cl_2.6H_2O$	DMF	60
6	$Cu^{II}(BF_4)_2$. H_2O	CH_3CN	90	12	$Co^{II}Cl_2.6H_2O$	Methanol	>99



Cytotoxicity Evaluation

	GFP A375		SKMEL-28	
COMPD	Avg IC_{50} (μM)±SD		Avg IC_{50} (μM)±SD	
P1	51.7	7.51	42.8	0.35
P2	54.3	1.6	42.6	1.48
P3	54.8	2.68	59.1	4.62
P4	55.9	6.35	55.3	12.67
P5	65.3	4.18	86.9	43.06
P6	113.5	3.31	47.6	1.65
P7	53.3	4.16	46	0.96
P8	55.3	3.82	175	12.53
P9	**25.8**	**2.7**	33.3	1.67
P10	85.9	13.83	155.2	0.07
P11	45.2	2.03	40.8	1.02
P12	55.3	2.55	43.7	2.68
P13	109.8	15.37	50	4.32
P14	65.4	5.13	42.7	4.03
P15	40.2	1.21	76	16.63
P16	57.8	6.46	301.1	
P17	73.5	3.83	24	1.97
P18	58.5	3.38	36	3.95
P19	46	0.98	39.1	2.31
P20	44.5	2.95	23.3	10.64
P21	48	2.13	19.3	2.41
P22	47.1	4.17	40.5	2.99
CELECOXIB	**26.9**	**2.7**	11.4	2.42

Conclusions

- We have developed two parallel approaches for the synthesis of substituted pyrazole heterocycles starting from hydrazines, and diketones.
- Microwave assisted synthesis approach is much faster, but metal-catalyzed approach is equally effective in terms of product yield.
- Pyrazole P9 seems to be equally potent as Celecoxib against A375 cells, but not against SKMEL-28.
- We are in the process of making pyrazole molecular hybrids to improve the anticancer activity.

Acknowledgements

We are grateful for the financial support from Louisiana Biomedical Research Network (LBRN), and University of Louisiana Monroe (ULM).