Decreasing the synthesis reaction time and toxicity of biologically active hetero (N-, P-, and F-) organics using green chemistry

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ABSTRACT

Stimulation of immunity of living organisms (immunocorrection) allows inducing their complex nonspecific resistance to many diseases of fungal, bacterial and viral origin, furthermore to other unfavorable environmental factors. For the purpose of synthetic search of potential immunocorrectors, it has been synthesized new α-aminophosphonates based on 1-phenylpiperazine and 1-benzhydrylpiperidine [1] using classical Kabachnik-Fields reaction conditions. These α-aminophosphonate compounds have properties of local anesthetics and show less toxicity when compared to known marketed medicines, which will be discussed in this study. Figure 1 shows scheme for the Kabachnik-Field reaction.

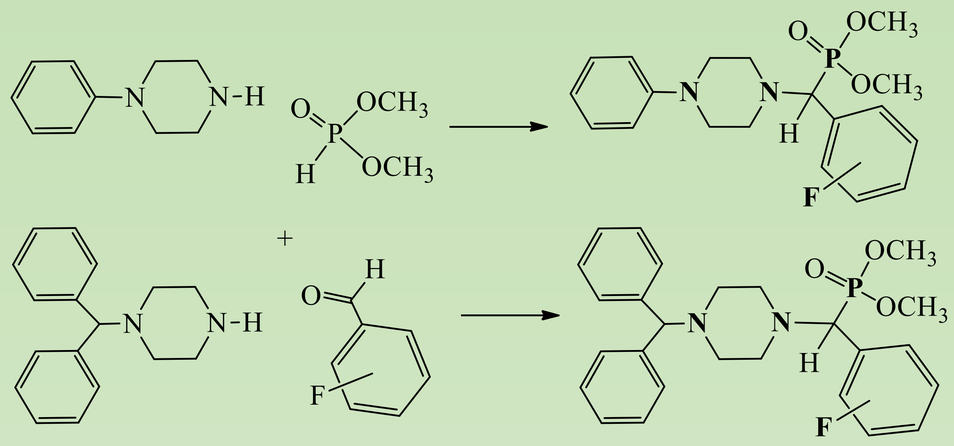


Figure 1. Scheme for the Kabachnik-Field reaction for the synthesis of α-aminophosphonates

OBJECTIVES

1. Decrease the reaction time of the synthesis of α-aminophosphonates by using microwave radiation
2. Exclude use of benzene from the synthesis reaction
3. Compare anesthetic properties of α-aminophosphonates with known medicines
4. Compare toxicity of α-aminophosphonates with known medicines

RESULTS and DISCUSSIONS

There are two main disadvantages of classical Kabachnik-Fields synthesis reaction, that are reaction time: 24 hours and more; and use of toxic and carcinogenic benzene. By using microwave radiation and ZnO, MgO as catalysts, it is possible to reduce the reaction time to 25 minutes and exclude the use of benzene from the reaction. Figure 2 shows the comparison between classical and microwaved reactions in terms of reaction time and yield (%).

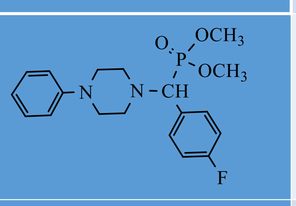
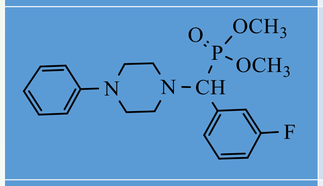
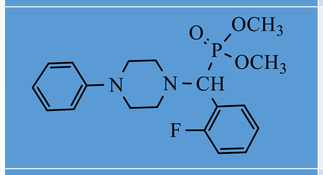
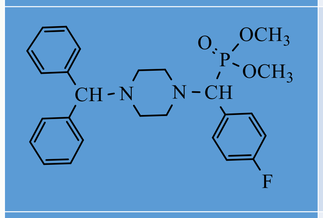
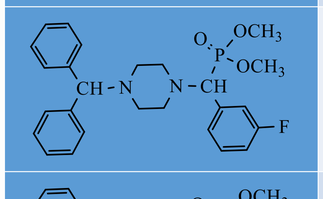
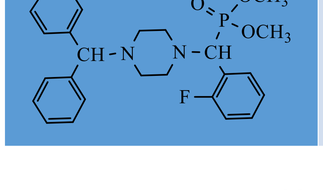
α-aminophosphonates	Classical reaction		Microwave radiation, MgO		Microwave radiation, ZnO	
	Yield, %	Time, h	Yield, %	Time, min	Yield, %	Time, min
	63,8	31	~95	25	~97	25
	61,9	37	~86	25	~85	25
	58,5	36	~59	25	~65	25
	82,9	30	~68	25	~61	25
	85,7	28	~73	25	~72	25
	90,3	29	~65	25	~71	25

Figure 2. Comparison table of reaction time and percent yield for classical and microwaved synthesis of α-aminophosphonates

RESULTS and DISCUSSIONS (cont.)

The anesthetic properties and toxicity level of synthesized compounds were studied according to the methodologies approved by the Pharmacology committee of Republic of Kazakhstan at National Medicinal University named after Asfendiyarov S.D. As a reference local anesthetics next medicines were chosen: lidocaine, novocaine and trimecaine. For infiltration anesthesia it was used guinea pigs (male) about 200-250 g. Anesthetic activity was evaluated 6-8 times for each chosen concentration for each sample and reference medicines by touching with blunt-edged needle 6 times every 5 minutes, in total during 30 minutes. The anesthesia level described as “anesthesia index”, maximum possible is 36. For evaluation of the conductive anesthesia modified tail-flick method was used to study duration of deep anesthesia and total duration of anesthetic effect. The toxicity level was studied on 18 mice, of same type, gender, age and weight 18-22 g, divided into 3 groups, 6 in each. Toxicity was evaluated by subcutaneously injecting aqueous solution 4% once. Statistical results of described studies can be observed from the Figure 3. Figure 3 includes comparison of lethal dose concentration (LD50), infiltration anesthesia and conductive anesthesia of α-aminophosphonates and reference medicines.

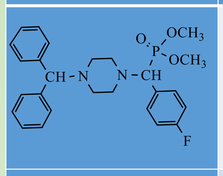
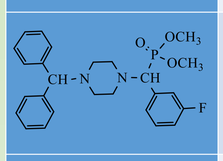
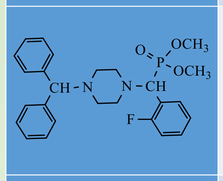
α-aminophosphonates and reference medicine	LD 50, ug/kg	Infiltration anesthesia			Conductive anesthesia	
		Anesthesia index	Deep anesthesia duration, min	Duration of anesthetic effect, min	Deep anesthesia duration, min	Duration of anesthetic effect, min
	624,9± 20,9	36,0±0	60,0±9,95	114,16±2,13	17,5±5,57	92,5±9,84
	815±16,5	30,0±6,02	59,16±5,4	102,5±7,18	30,0±6,73	117,5±4,62
	575±13,8	36,0±0	70,83±4,74	124,16±3,28	50,0±10,0	172,5±8,2
Trimecaine	375±3,1	32,1±1,5	20,0±1,7	38,3±10,5	47,3±8,4	56,9±12,8
Lidocaine	230±35,7	23,1±0,9	14,2±0,8	30,8±0,8	65,0±18,4	90,8±18,4
Novocaine	480±1,0	25,±1,0	10,0±1,2	29,1±1,5	35,2±7,1	42,3±13,6

Figure 3. Comparison table of lethal dose concentration (LD50), infiltration anesthesia and conductive anesthesia of α-aminophosphonates and reference medicines.

CONCLUSIONS

Using principles of green chemistry it was aimed to reduce the synthesis reaction time by using microwave radiation and exclude use of toxic and carcinogenic benzene, which is used in classical Kabachnik-Fields reaction to produce α-aminophosphonates showing local anesthetic properties. It can be concluded that, using those approaches of green chemistry it is possible to synthesize local anesthetic active substances which have better anesthesia parameters and lower toxicity level when compared to marketed medicines of known manufacturers.

REFERENCES

1. Begimova G.U., Akhmetsadyk O.E., Praliyev K.D., Yu V.K. Dimethyl[(3,4-dimethoxyphenyl)(4-phenylpiperazine-1-yl)methyl]phosphate: synthesis and structure // Chemical Journal of Kazakhstan – 2016. – № 1. – pp. 179-184.

2. Mashkovskyi M.D., Lekarstvennye sredstva, M., 1998, part 1, pp. 329-330, Lidocaine; pp. 326-328, Novocaine; 330-331, Trimecaine

3. Patent #103395 Authors: Olzhas Akhmetsadyk, Kaldybai Praliyev, Valentina Yu, Aigul Malmakova, Gulshat Dalzhanova, Elmira Satbaeva, Marzhan Amirkulova, Dilyara Kadyrova. Patent owner: Institute of chemical sciences named after A.B. Bekturov.

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